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14. ABSTRACT
Background: Restless Legs Syndrome (RLS) is a commonly under diagnosed organi cause of insomnia. There is evidence that insomnia leads to psychic distress which impacts healh care utilization. Purpose: To examine a proposed model which links RLS to insomnia, and insomnia to reduced mental health and increased utilization. Scope: To estimate the prevalence of RLS, insomnia, mood disorders, and substance abuse; quantify the proportion of mood disorders and substance abuse which are attributable to RLS and insomnia; document the diagnosis of RLS and insomnia; and estimate the association of RLS and insomnia to health care utilization and health related quality of life. Methods: A cross-sectioanl surey of a representative sample of Ohio VA clients using telephone interviews and data extracted from medical records. One year follow-up of health care utilization using postal questionnaire and medical records. Results: The prevalence of RSL and insomnia are high (22% and 16% respectively) as are mental health disorders (major depression, 20%; anxiety disorder, 12%; phobias, 14%; panic attack, 6%; alcohol dependence, 3%). Less than 5 % of RLS was documented in the medical record. RLS is associated with insomnia (PR = 1.5, p<.001) and 20% of the insomnia may be attributed (PAR) to RLS. As RLS is untreated in this population, the burden of insomnia might be reduced by 20% with effective treadtment of RLS.

15. SUBJECT TERMS
Restless Legs Syndrome, Insomnia, Depression, Mood disorders, Utilization, Veterans, Epidemiology

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INTRODUCTION

Restless Legs Syndrome (RLS) is a neurological disorder characterized by unpleasant, abnormal feelings in the legs and occasionally arms which occur at rest and when initiating sleep. The sufferer experiences an uncontrollable urge to move in order to relieve symptoms. RLS interferes with the ability to fall asleep or to maintain sleep. The resulting sleep deprivation can interfere with family life, social activities, and job performance. (1) We hypothesize that RLS has a high prevalence in the veteran community and is under diagnosed. We also hypothesize that undiagnosed and untreated RLS is associated with an unknown, but measurable proportion of the insomnia in any population. An association between insomnia and mood and anxiety disorders is well documented, as is the association between these mental health disorders and increased health care utilization. (2;3) In this research, we therefore propose an underlying model in which RLS contributes to insomnia; and insomnia contributes to diminished mental health status. Diminished mental health status in turn may lead to increased health care utilization.

The current research, which we are calling the Veterans Sleep Study, is a study of the prevalence and outcomes of RLS among patients of the Veterans Administration health care system in northern Ohio. The specific goals of the research are the following:

- To estimate the prevalence of Restless Legs Syndrome and insomnia;
- To determine in the VA population the proportion of insomnia that is attributable to RLS;
- To estimate in the VA population the strength of the association of insomnia and RLS with depression, anxiety, and substance abuse adjusting for comorbid health conditions;
- To estimate in the VA population strength of the association of insomnia and RLS with health related quality of life adjusting for comorbid conditions;
- To document the current level of diagnosis of insomnia and RLS in the VA population;
- To document the level of health care utilization at baseline interview and at one year follow-up associated with insomnia and RLS adjusting for comorbid health conditions;
- To assess the validity of the questionnaire instrument using interview by a trained clinician as the gold standard.

BODY OF REPORT

STATEMENT OF WORK

The following is the revised statement of work which was submitted on December 18, 2002 and approved by email on February 6, 2003. In April, 2004, Task 6 was added to the project. The report of our accomplishments with regard to these items follows.

Task 1: Estimate the prevalence of Restless Legs Syndrome, insomnia, mood and anxiety disorders, and substance abuse in persons who have scheduled primary care appointments at a Veterans Administration Community Based Outpatient Clinic (CBOC) in northeast Ohio. Document the current level of diagnosis of insomnia and RLS in the VA population.

a) Hire and train study personnel (Months 1-2)
b) Recruit 1914 study members at CBOC's (Months 3-8)
c) Conduct computer assisted telephone interviews with 1914 Veterans Administration clients. (Months 4-10)
d) Extract problem lists and time 1 utilization data from 1914 electronic medical records. (Months 6-12)
e) Data cleaning and analysis (Months 13-21)
f) Manuscript preparation (Months 20-24)

Task 2: Estimate in the northern Ohio VA population the strength of the association of RLS with insomnia after adjusting for comorbid health conditions. Determine the proportion of insomnia that is attributable to RLS. Estimate in the VA population the strength of the association of insomnia with depression, anxiety, and substance abuse adjusting for comorbid health conditions. Determine the proportion of psychic distress that is attributable to insomnia. Estimate in the VA population strength of the association of insomnia and RLS with health related quality of life adjusting for comorbid conditions.

a) Data analysis (Months 22–30)
b) Manuscript preparation (Months 30-36)

Task 3: Document the level of health care utilization at baseline interview and at one year follow-up associated with insomnia and RLS adjusting for comorbid health conditions.

a) Conduct interviews by mail with 1914 VA clients to determine health care utilization one year after baseline interview. (Months 16-23)
b) Extract time 2 utilization data from 1914 electronic medical records (Months 16 – 23)
c) Data entry, cleaning, and analysis (Months 18 - 30)
d) Manuscript preparation (Months 30 - 36)

Task 4: Assess the validity of the RLS questionnaire using interview by a trained clinician as the gold standard.

a) Recruit study members who are patients at the Akron CBOC and conduct clinical assessment (Months 7 - 18)
b) Analyze data (Months 19 - 20)
c) Manuscript preparation (Months 21 - 24)

Task 5: Assess the external validity of the study sample with respect to the population of VA patients who have had a visit in the past year.

a) Extract population data from electronic patient record system (Months 13-14)
b) Data analysis (Months 15-16)
c) Manuscript preparation is part of *Task 1.*

Task 6: Conduct a pilot study of an aerobic exercise intervention to improve sleep quality among RLS patients by moderating their RLS symptoms.

a) Identify RLS cases, confirm diagnosis and recruit up to 30 study members. Hire and train staff. (Months 25 – 27)
b) Compliance trial. (Month 28)
c) Conduct 3 month crossover study. 3 month intervention and 3 month control condition. (Month 29-34)
d) Analyze data and prepare report. (Month 35-36)

ACCOMPLISHMENTS OF THE RESEARCH.

This report is cumulative and incorporates material from previous reports.

Task 1

Estimate the prevalence of Restless Legs Syndrome, insomnia, mood and anxiety disorders, and substance abuse in persons who have scheduled primary care appointments at a Veterans Administration Community Based Outpatient Clinic (CBOC) in northeast Ohio. Document the current level of diagnosis of insomnia and RLS in the VA population.

Contributes to research goals:

- To estimate the prevalence of Restless Legs Syndrome and insomnia;
- To document the current level of diagnosis of insomnia and RLS in the VA population;

Task 1.a Hire and train study personnel.
Task 1.b Recruit 1914 study members at Community Based Outpatient Clinics.
Task 1.c Conduct computer assisted telephone interviews with 1914 Veterans Administration clients.
Task 1.d Extract problem lists and Time 1 utilization data from 1914 electronic medical records.
Task 1.e Data cleaning and analysis
Task 1.f Manuscript preparation

Tasks 1.a-e are complete.
Task 1.f. Manuscript preparation is underway.

Methods

Interview data

Study member recruiting and interviewing ended in August, 2004. 1761 veterans were recruited and interviewed for the research. An additional 351 veterans were recruited and completed the consent procedure but either declined to participate when later contacted for the telephone interview or could not be reached by telephone. Table 1 shows the age and gender distribution of these study members along with the originally planned sample size in each age/ gender group.

As can be seen from Table 1, our recruiting efforts were successful in 6 of 9 age groups. We were unsuccessful in recruiting our planned numbers among men age 40 and younger, and women over age 50. When it became apparent to us that the final sample size would be reduced, we made a decision to over sample in some of the more available age/gender groups in order to retain overall statistical power.

	Age Group	Original Sample Size	Persons Recruited	Completed Interviews
Men	18-30	115	34	26
	31-40	177	82	59
	41-50	177	247	184
	51-60	236	345	282
	61-70	236	305	252
	71-80	236	350	298
	81 +	290	360	311
Women	18-50	157	221	185
	51+	290	175	164
Total		1914	2119	1761

Table 1.1 Planned and final sample size

Problem list data

Our purpose for the data from the problem lists is case-mix adjustment. In order to obtain valid estimates of the association between sleep disorders and mental health, health related quality of life, or health care utilization, adjustment for current health status is required. Our intent had been to use the problem list file available in the computerized patient record system (CPRS) to do that adjustment.

A detailed examination of a sample of medical records in comparison to the problem lists indicated that the problem lists contained in the medical record were not sufficiently complete for our purposes. We, therefore, obtained the data from all outpatient visits made by study members in the 18 months prior to the Time 1 interview. The ICD codes for all problems managed during those office visits have been merged with the previously obtained problem list data to obtain a more complete list of current health conditions at Time 1 interview.

These data were processed using the Johns Hopkins Case-Mix Adjustment software to assign ambulatory diagnostic groups (ADG's) to each study member. Appendix Table A.10 shows the frequency distribution of assigned ADG's stratified by gender and age.

Health care utilization data

The following have been obtained:

Prescription drugs.
Medications active at the time of the interview
Drug class
Date of prescription
Quantity
Number of refills
Status of prescription (active, suspended, discontinued, or expired)

Medications prescribed in a window from six months prior to the interview date to six months after the interview were identified. We were concerned that if we used only the prescriptions one month prior to the interview date that we would miss active medications taken infrequently. This information in conjunction with the quantity prescribed allows us to pick up infrequently used, but current prescriptions.

Clinic visits
Clinic visits completed in the month prior to the interview
Type of appointment: lab, radiology, primary care, mental health, physical therapy, optometry, podiatry, etc.
Date of appointment
Stop code – a VAMC indicator of the type of provider seen, multiple stops per date
CPT code – a VAMC procedure code, multiple CPT codes per stop

Hospital admissions
Admissions to VA facility in the month prior to the interview
Principle diagnosis
Date of admission
Date of discharge
Length of stay

Surgical procedures
Procedures and surgeries in the month prior to the interview
ICD code
Date of procedure or surgery
Inpatient or outpatient

Laboratory
Laboratory tests
Test code
Lab tests within the month prior to the interview
Date of tests
Test result

Radiology
Radiology visits
Imaging reports within the month prior to the interview
Type of imaging procedure
Date of test

Each patient encounter, i.e., each office visit, laboratory procedure, prescription refill etc. generates a computerized patient record. Computer programs have been written to collapse and summarize this large amount of data.

Diagnosis of RLS and insomnia
We searched inpatient and outpatient medical record data for ICD-9 codes associated with insomnia (307.40-307.49 Specific disorders of sleep of non-organic origin and 780.50-780.59 Sleep disturbances) and RLS (333.99).

Results

Appendix A contains detailed data tables. Table A.1 shows the descriptive characteristics of the study members. Eighty percent of the sample are men. Most are White/Caucasian (88%) although 8% are African American and 3% are Native American. Almost half (46%) of the

sample have at least some college education. An alarming 80% of the sample are overweight or obese and 22% are currently smokers.

Veterans who receive primary care from the VAMC report a high prevalence of symptoms which meet the ILRSSG criteria for a diagnosis of RLS.(4) The prevalence estimates that are shown incorporate the coding criteria which were developed in our Validation Study, see Task 4 and the manuscript included in Appendix C.

Based on the outcome of Task 4, we define an RLS case as anyone who reports 3 or more of the IRLSSG criteria. This definition which will be titled "Definite and Probable Cases" resulted in the most favorable balance of sensitivity and specificity. We will also discuss some results restricted to persons who reported all IRLSSG required symptoms ("Definite Cases").

The overall prevalence of definite and probable RLS is 46% among women and 35% among men. The overall prevalence of definite RLS is 32% among women and 20% among men. These estimates are extraordinarily high. We used the method of Rogan and Gladen (5) to adjust these prevalence estimates using the sensitivity and specificity estimates obtained in Task 4. This adjustment increased the estimated prevalence of definite and probable RLS to 67% among women and 44% among men. The prevalence of definite RLS increased to 54% among women and decreased to 9% among men. These prevalence estimates are very high and we are evaluating possible explanations of the estimates.

Figures 1 to 3 show the prevalence of RLS, insomnia and day time sleepiness by age and gender. The data from which Figures 1 to 3 were prepared can be found in Appendix A, Tables A.2 to A.4. Ninety-five percent confidence intervals are shown for all estimates. Among women, the prevalence of definite RLS peaks between the ages of 30 and 50; among men, prevalence peaks between ages 50 and 60. Among both men and women between the ages of 30 and 59, at least half of respondents reported some RLS symptoms at least 2 days a month.

The prevalence of insomnia and daytime sleepiness are similarly high. Overall, 13% of study members reported moderate insomnia and 3% reported severe insomnia. Eighteen percent of respondents report moderate daytime sleepiness and 7% report severe day time sleepiness.

Figures 2 and 3 show these outcomes stratified by age and gender. While women report higher rates of RLS and insomnia, men report higher rates of excessive daytime sleepiness, especially severe sleepiness. Women age 30 to 50 also report the highest rates of insomnia. Among men, peak levels of insomnia occur in ages 40 to 60. Younger women and middle aged men report the highest levels of daytime sleepiness.

We also found that a large proportion of RLS cases have another health condition which may be the underlying cause of their RLS symptoms (secondary RLS) (Table A.6). These conditions include: anemia, kidney disease, other movement disorders, neuropathy, and SSRI use. Although it impossible to confirm this with our data, the high prevalence of these conditions may be partially responsible for the high prevalence of RLS in the VA population. We plan additional data analysis in which primary and potentially secondary RLS are examined separately.

Figure 1. Prevalence of RLS

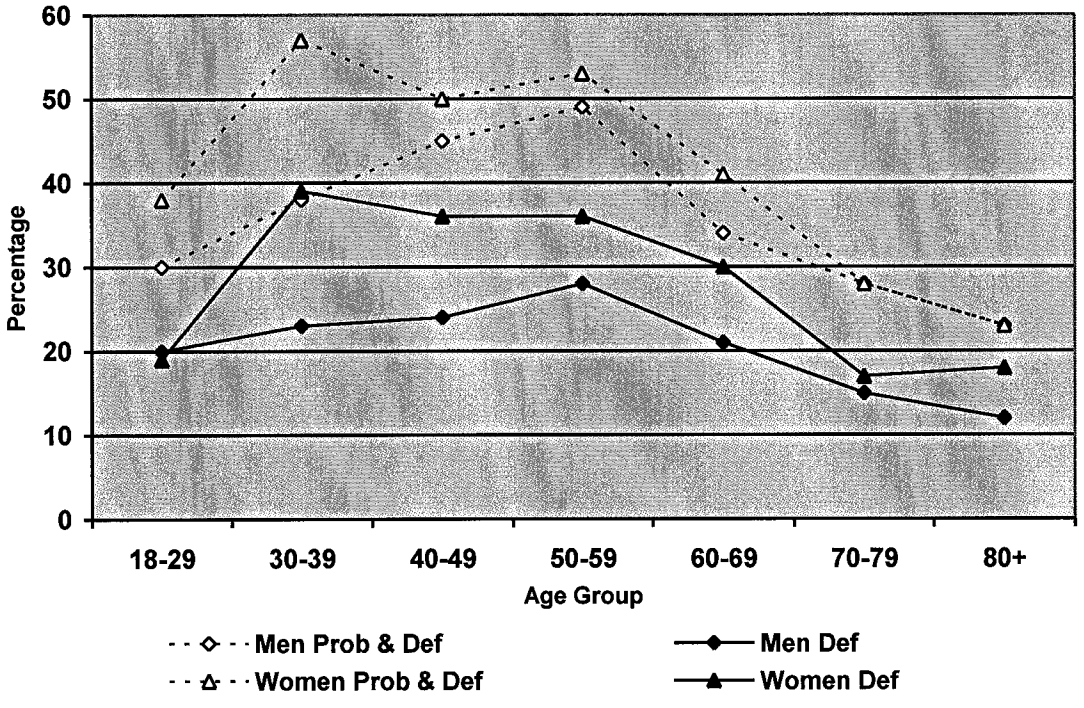


Figure 2. Prevalence of Insomnia

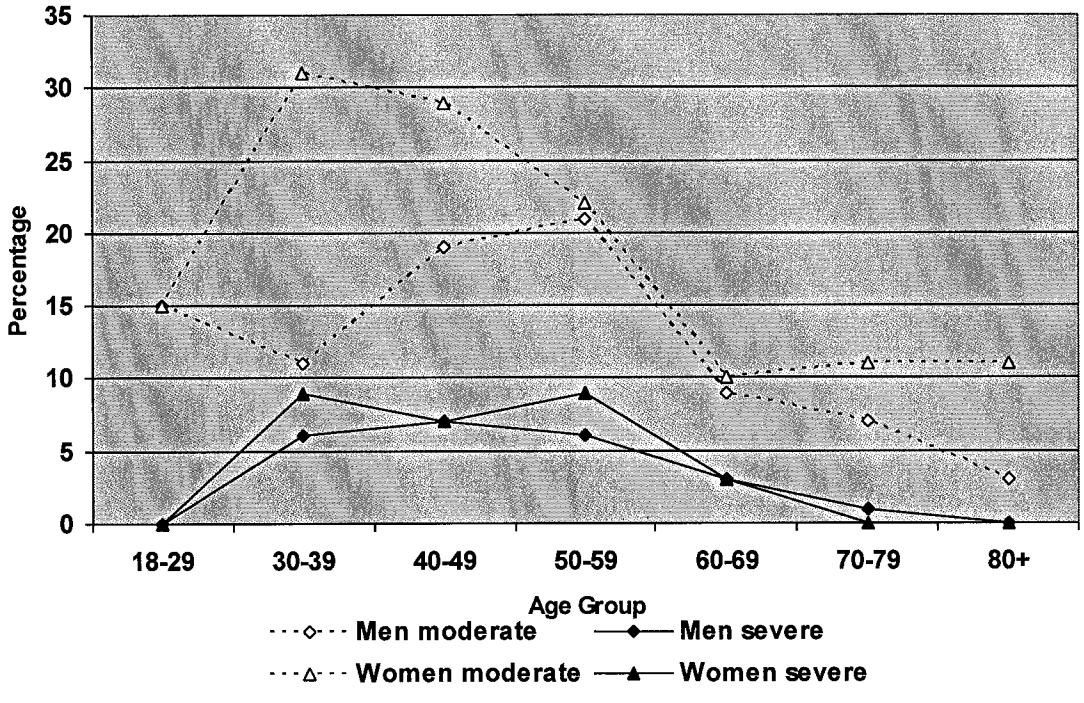
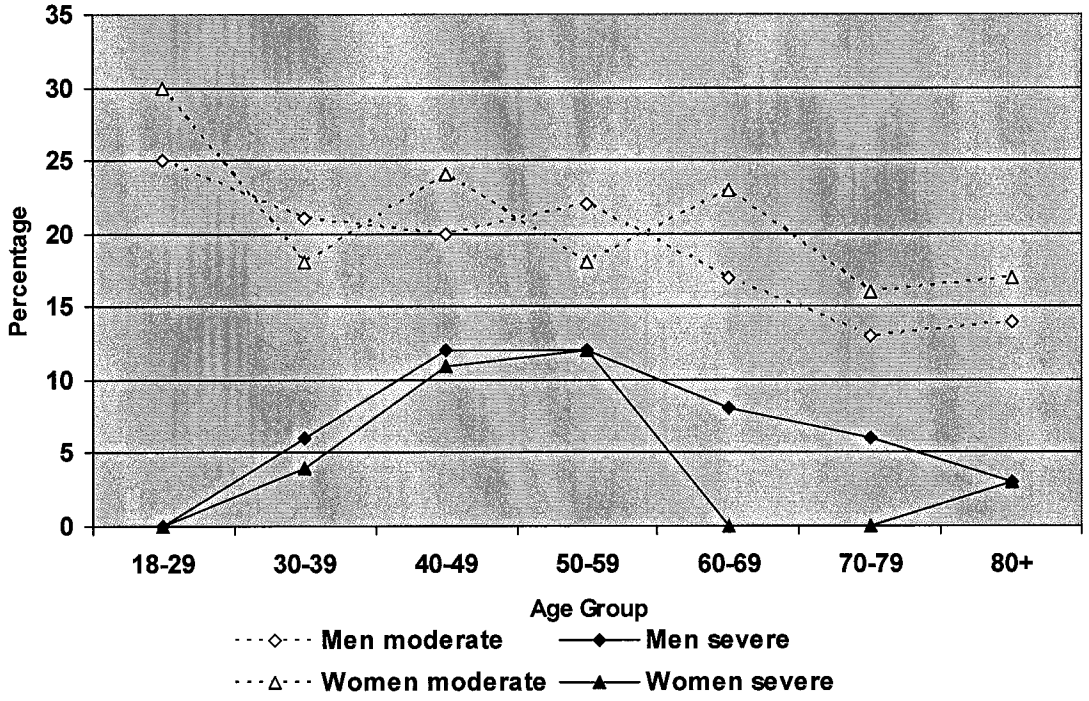


Figure 3. Prevalence of Daytime Sleepiness



In spite of the high prevalence of RLS, insomnia, and excessive daytime sleepiness found by this survey, the level of diagnosis of these conditions found in the VAMC medical records of the study members is relatively low. Four percent of persons who definitely meet the criteria for RLS and 3% of those who probably meet the criteria for RLS showed a diagnosis of RLS anywhere in their medical record. Diagnosis of insomnia and daytime sleepiness was better recorded in the VA medical record. Twenty-nine percent of respondents who reported moderate or severe insomnia had any sleep diagnosis in their medical record (26% severe; 30% moderate). Thirty-six percent of respondents who reported severe daytime sleepiness and 22% of persons who had moderate daytime sleepiness had any sleep diagnosis in their medical record. These data can be found in Appendix A, Tables A.7 through A.9.

Estimates of mental health status, CIDI scores. We used the CIDI short form (SF) which was developed by the World Health Organization. The CIDI contains subscales to evaluate major depression, generalized anxiety disorder, specific phobia, social phobia, agoraphobia, panic attack, alcohol dependence, and drug dependence. Each CIDI subscale yields a score which can be interpreted as the probability that a respondent with a particular response profile would meet the full diagnostic criteria for the disorder if given the full CIDI form. The full CIDI classifies respondents using the DSM-IV criteria for the above mental health conditions. The CIDI-SF asks about symptoms within the past year and thus produces an estimate of one year prevalence.(6) (7)

Detailed data on the proportion of study members who met the DSM-IV criteria for 6 mental health conditions and 2 substance along with alcohol and drug dependence are shown in Table

A.5 in Appendix A. Table 1.2 summarizes the prevalence of mental health diagnoses by gender. Diminished mental health status is common in this sample. Major depression is the most common condition (Prevalence = 20%). In addition, more than 10% of the sample suffer from generalized anxiety disorder or a specific phobia.

	Number and percent meeting CIDI criteria for DSM-IV diagnosis.					
	Males		Females		All	
	Number	%	Number	%	Number	%
Major Depression	238	17	114	33	352	20
Generalized Anxiety Disorder	136	10	65	19	201	12
Specific Phobia	170	12	79	23	249	14
Social Phobia	69	5	41	12	110	6
Agoraphobia	47	3	28	8	75	4
Panic Attack	64	5	43	12	107	6
Alcohol Dependence	44	3	11	3	55	3
Drug Dependence	14	1	8	2	22	1

Table 1.2 Prevalence of mental health conditions and substance abuse by gender.

Figures 4 to 9 show the age/ gender distributions of DSM IV mental health diagnoses in more detail. The levels of alcohol and drug dependence were relatively low and are not shown in the figures.

Figure 4. Prevalence of Major Depression

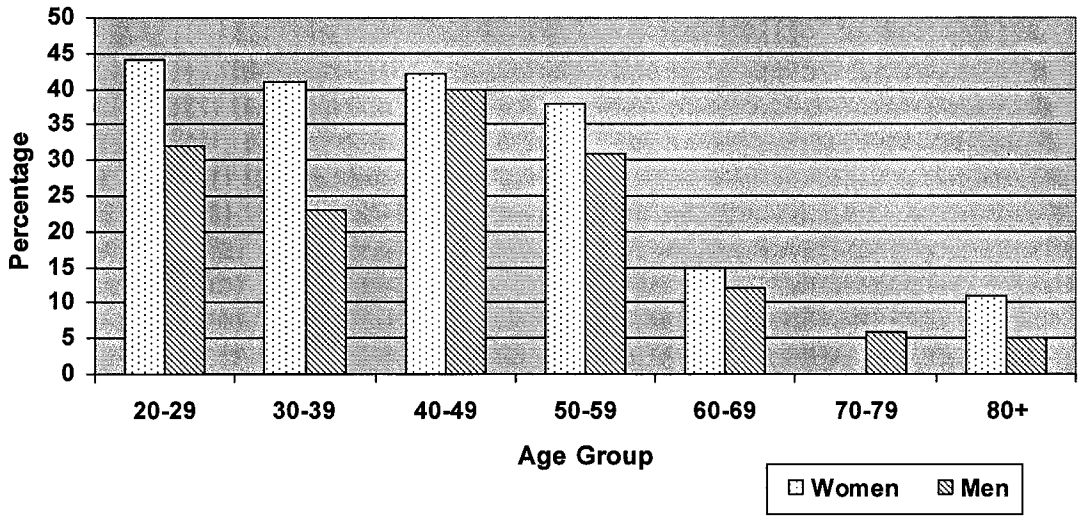


Figure 5. Prevalence of General Anxiety Disorder

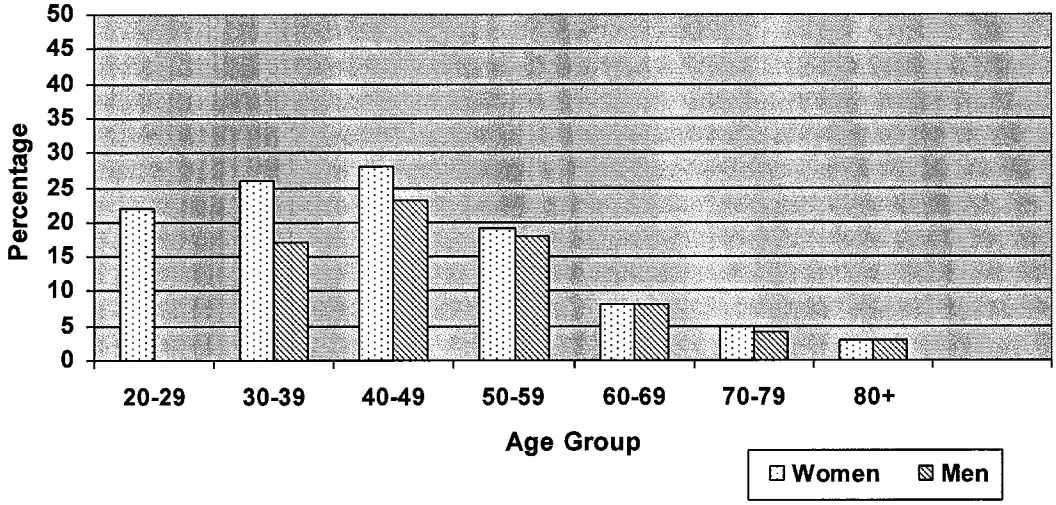


Figure 6. Prevalence of Specific Phobia

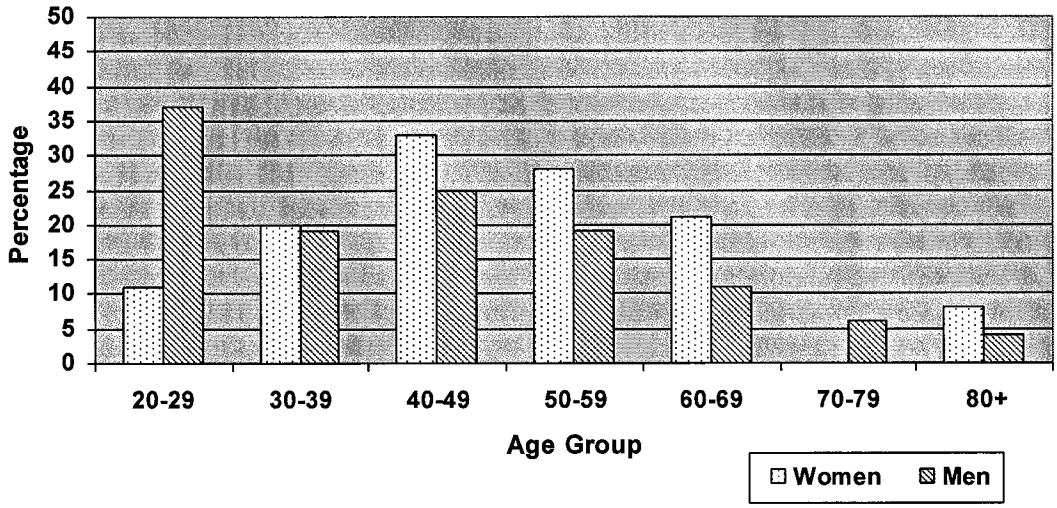


Figure 7. Prevalence of Social Phobia

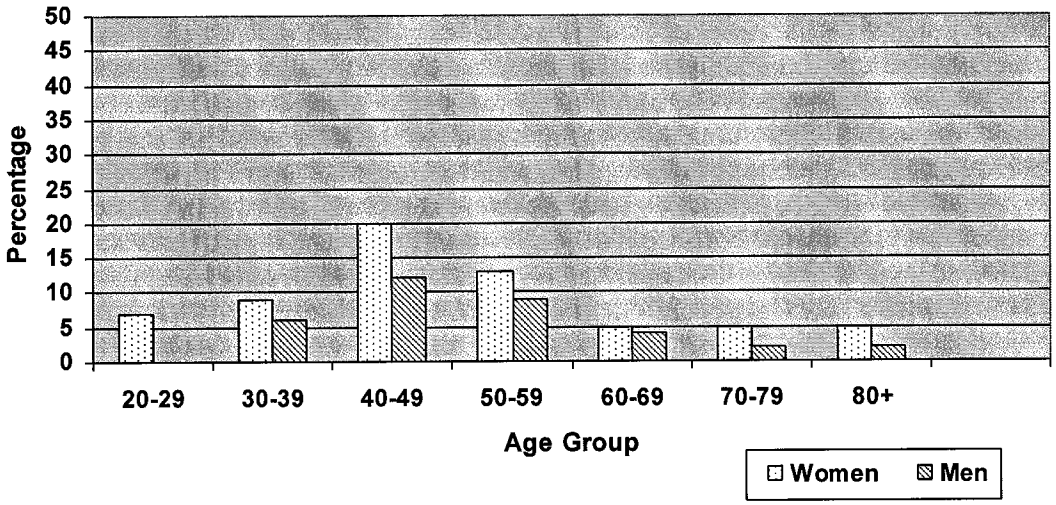


Figure 8. Prevalence of Agoraphobia

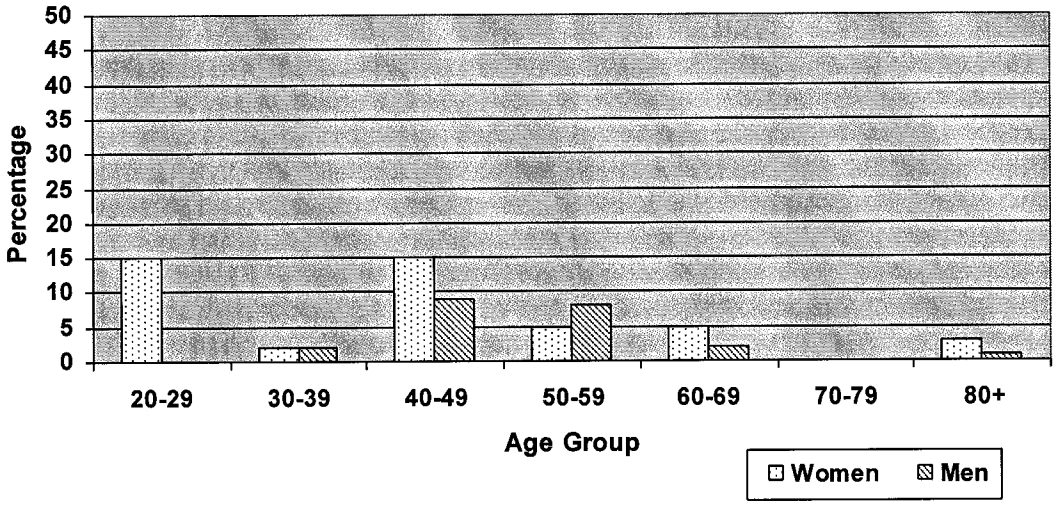
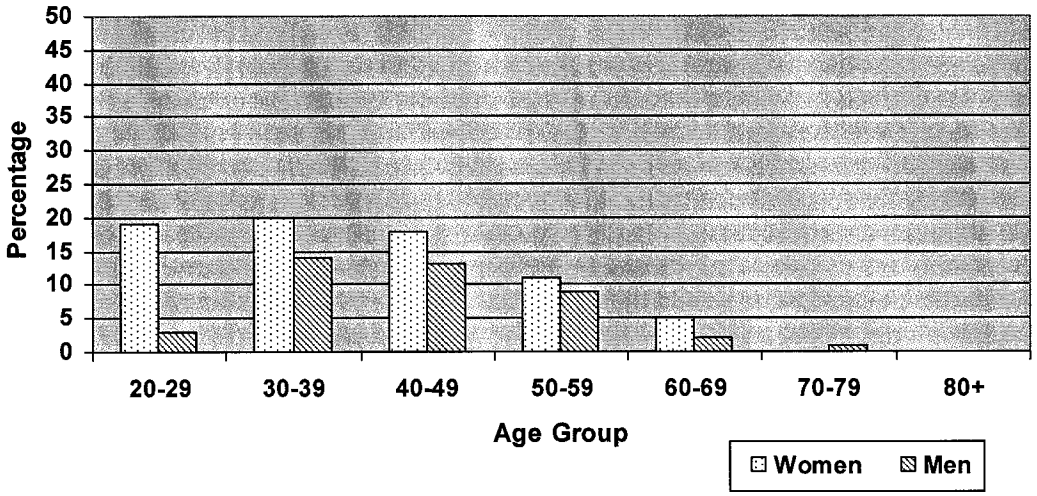


Figure 9. Prevalence of Panic Attack



The high prevalence of mental health conditions in this sample, especially at younger ages, is a unique feature of patients who obtain health care from the veterans affairs system. Because of income and disability restrictions, younger patients are more likely to show higher levels of morbidity than older patients. Depression and panic attacks are especially likely to develop subsequent to a diagnosis of insomnia.(8)

The high prevalence of mental health conditions in this VA sample highlights the importance of identifying and intervening on factors which may contribute to these mental health conditions.

Task 2:

Estimate in the northern Ohio VA population the strength of the association of RLS with insomnia after adjusting for comorbid health conditions. Determine the proportion of insomnia that is attributable to RLS. Estimate in the VA population the strength of the association of insomnia with depression, anxiety, and substance abuse adjusting for comorbid health conditions. Determine the proportion of psychic distress that is attributable to insomnia. Estimate in the VA population strength of the association of insomnia and RLS with health related quality of life adjusting for comorbid conditions.

Contributes to research goals:

- To determine in the VA population the proportion of insomnia that is attributable to RLS;
- To estimate in the VA population the strength of the association of insomnia and RLS with depression, anxiety, and substance abuse adjusting for comorbid health conditions;
- To estimate in the VA population strength of the association of insomnia and RLS with health related quality of life adjusting for comorbid conditions;

Task 2.a Data analysis.
Task 2.b Manuscript preparation.

Data Analysis Methods

The data required for Task 2 were obtained in Task 1 and include data on insomnia (ISS scores), RLS (John Hopkins TDI scale), day time sleepiness (Epworth sleepiness scale), mental health data (CIDI scales) and health related quality of like (HRQL; the VA SF36). The data required for case-mix adjustment were obtained from the interview (demographic data) and the medical record (co-morbid health conditions).

Three case-mix adjustment methods to control confounding by health status with available software were researched: Johns-Hopkins ACG Case-Mix System, DxCG Software (DxCG, Inc.), and the Medicare Principal Inpatient Cost Group (PIP-DCG) Model. The input data for each patient that are required by all three methods are essentially the same: a patient identification code, gender, age (or DOB), and ICD-9 codes. All three methods then take this information and create various levels of patient groupings based diagnosis, which are then input, along with age and gender, into regression models to predict health care costs at the patient level.

Based on this research, the Johns-Hopkins ACG Case-Mix System (Version 6.0) was selected and a research license was purchased. This software produces two levels of patient groups: diagnosis clusters called Aggregated Diagnostic Groups (ADG) and Adjusted Clinical Groups (ACG).

Every ICD-9-CM code given to a patient was placed into one of 32 ADGs. Patients with multiple diagnoses could be assigned to more than one ADG. Based on the ADGs assigned and age and gender, the ACG System uses a branching algorithm to place patients into one of 93 (depending on system options set) discrete ACGs. Each patient belongs to only one ACG. Individuals within a given ACG have experienced a similar pattern of morbidity and resource consumption.

The data required for the case-mix adjustment were obtained from the participants' problem list and office visit data (see Task 1.d). The distribution of assigned ADG codes is shown in Table A.10.

The primary method for case-mix adjustment in this research was based on indicator variables for each of the ADGs (1 = present, 0 = absent), which were included as predictors in multivariable models. Demographic variables (age, gender, race, education) and the Physical Composite Scale (PCS) and Mental Health Composite Scale (MCS) were also used for case-mix adjustment.

We used Poisson regression to model the relative risk of insomnia or daytime sleepiness in the presence of exposure. This analysis was adjusted for demographics, ADG codes and the PCS and MCS. Surprisingly, few ADG codes were strongly related to insomnia or daytime sleepiness. The PCS explained additional variation in both dependent variables in models that contained the related ADG codes and was consistently included in models. When modeling mental health dependent variables (e.g. CIDI scales) mental health related ADG groups were excluded from the list of independent variables.

Results.

Estimates of health related quality of life, the SF 36 scale.
Figures 10 to 12 show descriptive information about the SF36 scores of the participants in the VA Sleep Study. We are using the VA SF36 scale as adapted by Kazis.(9) Figure 10 shows the distribution of SF36 scores obtained in the current VA Sleep Study compared to data from the Veterans Health Study and to a national SF 36 sample.(10) Participants in the VA Sleep Study appear to report better health related quality of life than participants in the Veterans Health Study. However, our data are not age and gender adjusted, so this conclusion may change. Both Veterans samples show poorer heath status than the US referent sample, although the patterns of better mental health than physical health status is consistent.

Figure 11 shows the distribution of SF36 scores from the Veterans Sleep Study stratified by gender. Men report better health related quality of life than women. Figure 12 shows the SF36 scores stratified by race and ethnicity. In this figure, persons who endorsed Hispanic ethnicity, also endorsed another race usually either white or African American. Differences between the racial and ethnic groups are uneven. Persons who reported white race had somewhat better mental health status. This is true for all of the mental health subscales. Persons who reported Native American race, had somewhat poorer physical health status. However, because of the small number of persons reporting Native American and Hispanic race or ethnicity, these estimates are likely to have wide confidence interval. The data from which these figures were prepared are included in Appendix A. Table A.11.

Veterans Sleep Study (VSS) Compared to the Veterans Health Study (VHS) and the National Survey of Functional Health (NSFH)

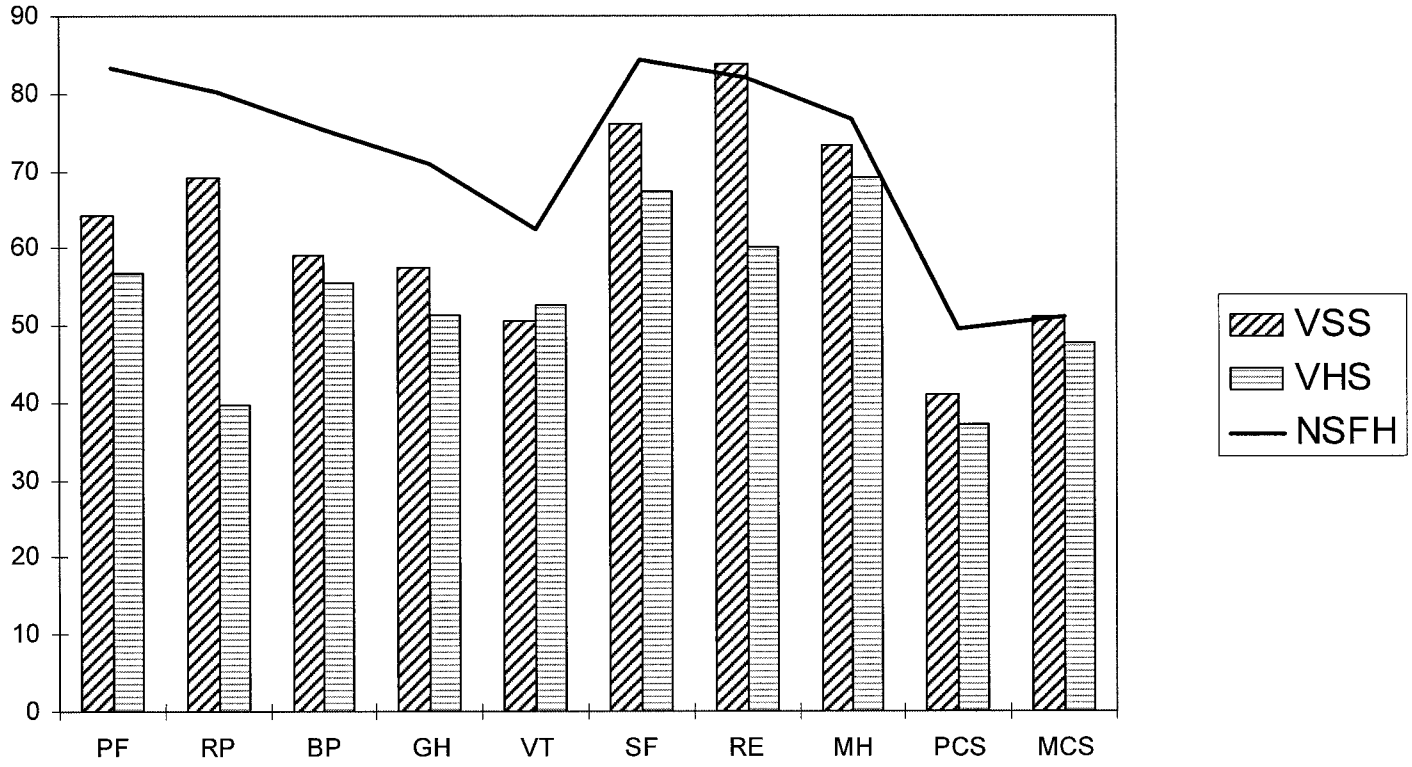


Figure 10. SF36 scores – Veterans Sleep Study, Veterans Health Study and national comparison sample.

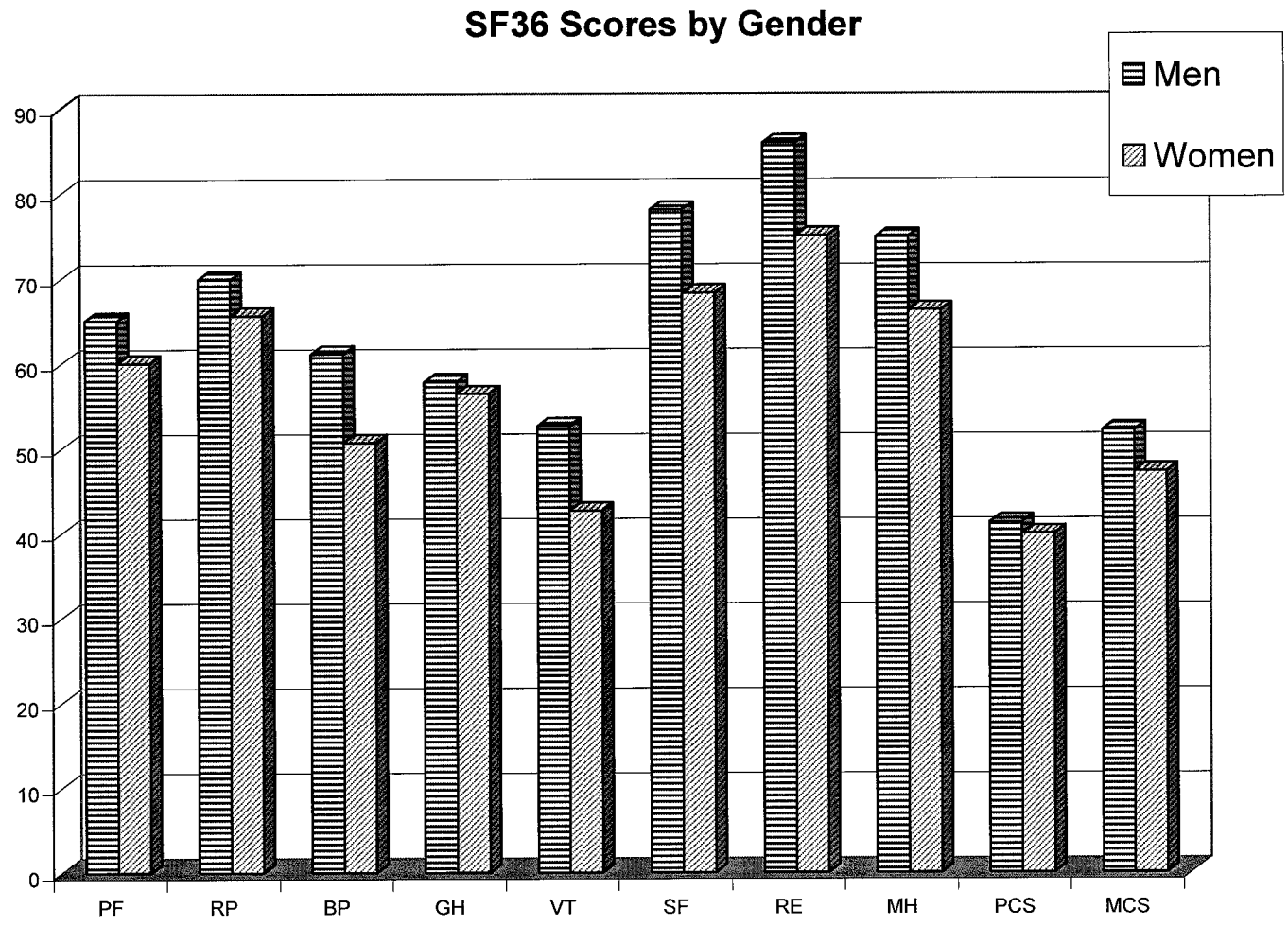


Figure 11. SF36 scores of participants in the Veterans Sleep Study, stratified by gender.

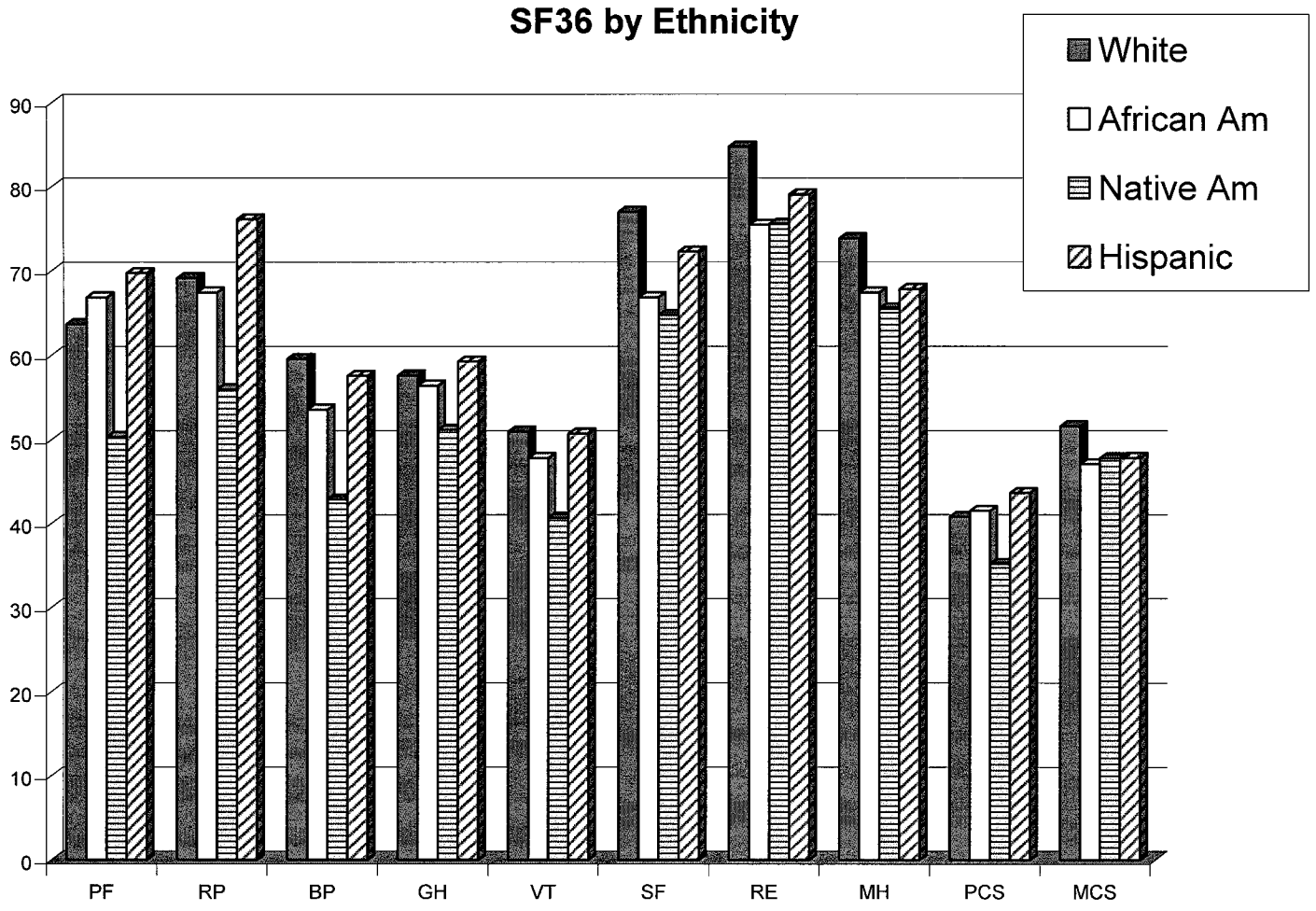


Figure 12. SF36 scores of participants in the Veterans Sleep Study, stratified by race and ethnicity.

Table 2.1 shows the correlations of the mental health composite (MCS) and Physical health composite (PCS) scales of the SF36 with the CIDI case probabilities. As expected there are strong correlations between the mental health scales of the SF36 and the probability of being judged a case using the CIDI scales. All CIDI scales are correlated with the MCS. The strength of the association is greatest for Major Depression and Generalized Anxiety. Correlations with the PCS are weaker. Because of the large sample size, nearly all correlations are statistically significant. Thus, the actual size of the correlation coefficient is more important than the p value in this context. The data for the detailed scales of the SF36 are shown in Appendix A, Tables A.12.a and A.12.b. The sign of the coefficients is negative because the scales are scored in different directions.

		Veterans SF36 Scales	
CIDI scale		Mental Health Composite (MCS)	Physical Health Composite (PCS)
Major Depression (prob. of case)	Rho P N	-0.52 <.0001 1723	-0.22 <.0001 1723
General Anxiety Disorder (case)	Rho P N	-0.45 <.0001 1701	-0.16 <.0001 1701
Specific Phobia (prob. of case)	Rho P N	-0.25 <.0001 1725	-0.11 <.0001 1725
Social Phobia (prob. of case)	Rho P N	-0.26 <.0001 1719	-0.11 <.0001 1719
Agoraphobia (prob. of case)	Rho P N	-0.23 <.0001 1719	-0.13 <.0001 1719
Panic Disorder (prob. of case)	Rho P N	-0.26 <.0001 1708	-0.09 .0003 1708
Alcohol Dependence (prob. of case)	Rho P N	-0.17 <.0001 1723	0.02 .36 1723
Drug Dependence (prob. of case)	Rho P N	-0.16 <.0001 1712	-0.04 .07 1712

Table 2.1. Correlation (Spearman's Rho) of SF36 composite scales with CIDI scales

Relative Risk and Population Attributable Risk of Insomnia and Day Time Sleepiness associated with RLS when controlled for co-morbid health conditions.

Table 2.2 shows the relative risk of insomnia in the presence of probable and definite RLS. The risk of moderate insomnia is multiplied by about 1.5 in the presence of RLS and this relationship is statistically significant. However, severe insomnia alone is unrelated to RLS in this sample.

	Risk Factor			
	RLS definite / probable		RLS definite	
Outcome	Relative Risk*	95% CI	Relative Risk	95% CI
Insomnia Severe	1.07	0.65, 1.77	0.99	0.57, 1.71
Insomnia Severe / Moderate	1.48	1.20, 1.81	1.48	1.21, 1.82
Insomnia Moderate	1.62	1.26, 2.07	1.66	1.30, 2.11
*Adjusted for age, gender, ADG scores, and PCS.				

Table 2.2 Relative Risk of insomnia in the presence of probable or definite RLS.

In contrast to the relationship of RLS and insomnia shown in Table 2.2, the data in Table 2.3 shows that, while insomnia is strongly related to day time sleepiness, RLS has little if any relationship to daytime sleepiness.

	Risk Factor							
	RLS definite		Insomnia Severe		RLS definite/ probable		Insomnia severe / moderate	
Outcome	RR*	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Day Sleep High	1.43	1.00, 2.04	2.88	1.84, 4.52	1.03	0.73, 1.45	3.47	2.26, 5.35
Day Sleep High/Mod	1.17	0.98, 1.40	1.50	1.18, 1.92	1.04	0.88, 1.23	1.91	1.59, 2.31
Day Sleep Mod	1.06	0.84, 1.35	0.82	0.49, 1.34	1.05	0.84, 1.30	1.43	1.11, 1.83
*Adjusted for age, gender, ADG scores, and PCS.								

Table 2.3 Relative Risk of daytime sleepiness in the presence of insomnia and RLS.

Table 2.4 shows the use of the relative risk estimates in several approaches to attributable risk calculation. Additional information is contained in Appendix Table A.13.

There are several published options available for calculation of the attributable risk %. Table 2.4 shows the results of two approaches. The approach of Levin uses estimates of population

prevalence. The approach of Kleinbaum uses the number of exposed cases rather than population exposure estimates. The column labeled "adjusted" uses prevalence estimates adjusted for the accuracy of the TDI based on the results of TASK 4.

Dr. Kristin Baughman, who is a member of the project staff, has summarized issues in attributable risk estimation in a presentation made to a NEOUCOM audience. A copy of the slides from her talk is included in Appendix D. Based on this work, we have concluded that Kleinbaum's estimates are the most appropriate for use in this analysis.(11;12)

Risk Factor: Probable or Definite RLS

Outcome	Prevalence of RLS Probable or Definite	RLS def/prob adjusted prevalence (using Task 4 data)	Proportion of Insomnia cases exposed to prob/def RLS	Relative Risk*	Levin's Attributable Risk using adjusted prevalence	Kleinbaum's Population Attributable Risk
Severe Insomnia	0.37	0.49	0.54	1.07	3.30	3.54
Mod / Severe Insomnia	0.37	0.49	0.57	1.48	18.95	18.65
Moderate Insomnia	0.37	0.49	0.58	1.62	23.19	22.35

Risk Factor: Definite RLS

Outcome	Prevalence of RLS Definite	RLS def adjusted prevalence (using Task 4 data)	Proportion of Insomnia cases exposed to RLS	Relative Risk *	Levin's Attributable Risk using adjusted prevalence	Kleinbaum's Population Attributable Fraction
Severe Insomnia	0.22	0.18	0.30	0.99	-0.18	-0.30
Mod / Severe Insomnia	0.22	0.18	0.37	1.48	8.02	12.09
Moderate Insomnia	0.22	0.18	0.39	1.66	10.71	15.66

* The Relative Risk estimates are adjusted for gender, age, ADG groups, and PCS.

Table 2.4 Proportion of moderate or severe insomnia which can be attributed to RLS.

This analysis indicates that approximately 15 to 20% of the moderate insomnia reported by the Veterans in this study is attributable to RLS and most of this is attributable to definite RLS. Only a small proportion of severe insomnia (0 to 3.5%) is attributable to RLS. These estimates represent the amount of insomnia that would be relieved if the RLS could be cured or effectively treated.

Because less than 4% of the RLS cases in this sample were previously diagnosed, virtually all of the RLS is accessible to intervention.

As there is no relationship between RLS and daytime sleepiness, we do not show the attributable risk analysis for that outcome.

Change in Mental Health Related Quality of Life associated with insomnia and RLS.

Least squares regression was used to estimate changes in mental health related quality of life (Mental health Composite Score) associated with severe or moderate insomnia and /or definite or probably RLS. This analysis was controlled for demographic factors and ADG groups. Table 2.5 shows the mean SF-36 MCS score in the presence and absence of insomnia and RLS.

Risk Factor		Predicted Mean MCS *	P value
Severe Insomnia	Present	37.7	P<0.001
	Absent	52.5	
Moderate Insomnia	Present	45.2	P<0.001
	Absent	52.9	
Definite RLS	Present	49.5	P<0.001
	Absent	52.4	
Probable RLS	Present	51.0	P=0.08
	Absent	52.2	
Severe Insomnia. & Definite RLS	Present	36.0	P<0.001 P<0.001
	Absent	50.8	
Any Insomnia. & Definite RLS	Present	41.8	P<0.001 P=0.003
	Absent	52.5	
Any Insomnia. & Any RLS	Present	42.1	P<0.001 P<0.001
	Absent	52.6	

* Model includes age, gender, education, PCS and ADG's.

Table 2.5 Predicted Mean MCS in the presence or absence of insomnia and RLS.

The data in Table 2.5 show that both definite RLS and any level of insomnia are statistically related to a decreased mental health related quality of life. However, the actual difference in MCS associated with RLS is small compared to the impact of insomnia. In the presence of insomnia, the

mean MCS is lowered more than a standard deviation (10 points). In the presence of RLS the mean MCS is lowered at most 3 points.

The implication of the data in Table 2.4 in combination with the data in Table 2.5 is that while 15 to 29% of insomnia in this population is attributable to RLS, RLS has no direct effect on mental health related quality of life, but rather acts through the effect on insomnia.

The relationship of DSM-IV defined mental health conditions with insomnia and /or RLS.

We used Poisson regression to estimate the relative risk of a DSM-IV mental health condition in the presence or absence of insomnia and or RLS. We also calculated the associated attributable risk %. Table 2.6 shows the results of this analysis.

Outcome	Risk Factors in Model	Relative Risk *	95% CI	Attributable Risk %
Major Depression	Severe Insomnia	2.2	1.8, 2.7	7.7
	Moderate Insomnia	1.6	1.3, 2.0	11.3
	Any Insomnia	2.2	1.8, 2.6	23.8
	RLS Definite	1.1	1.0, 1.4	3.8
	RLS Probable	1.0	0.8, 1.3	0.7
	Any RLS	1.2	1.0, 1.4	6.5
	Severe Insomnia & RLS Definite **	2.2 1.2	1.8, 2.7 1.0, 1.4	7.7 4.0
	Any Insomnia RLS Definite	2.2 1.1	1.8, 2.6 0.9, 1.3	23.6 1.4
	Any Insomnia Any RLS	2.2 1.1	1.8, 2.6 0.9, 1.3	23.7 2.9

Outcome	Risk Factors in Model	Relative Risk *	95% CI	Attributable Risk %
Generalized Anxiety Disorder	Severe Insomnia	2.5	1.9, 3.4	10.2
	Moderate Insomnia	2.0	1.5, 2.7	18.8
	Any Insomnia	3.1	2.3, 4.3	36.7
	RLS Definite	1.4	1.1, 1.9	10.8
	RLS Probable	1.2	0.9, 1.6	4.0
	Any RLS	1.6	1.2, 2.1	22.4
	Severe Insomnia & RLS Definite	2.5 1.4	1.9, 3.3 1.1, 1.9	10.2 10.9
	Any Insomnia RLS Definite	3.0 1.3	2.2, 4.1 1.0, 1.7	36.1 8.5
	Any Insomnia Any RLS	3.0 1.5	2.2, 4.1 1.1, 2.0	36.1 19.7
Outcome	**Risk Factors in Model**	**Relative Risk ***	**95% CI**	**Attributable Risk %**
Panic Attack	Severe Insomnia	1.9	1.1, 3.3	6.1
	Moderate Insomnia	1.5	1.0, 2.2	10.0
	Any Insomnia	1.9	1.3, 2.8	20.2
	RLS Definite	1.6	1.1, 2.2	14.0
	RLS Probable	1.0	0.7, 1.6	0.4
	Any RLS	1.6	1.1, 2.3	22.4
	Severe Insomnia & RLS Definite	1.9 1.6	1.1, 3.4 1.1, 2.6	6.2 14.3
	Any Insomnia RLS Definite	1.8 1.5	1.2, 2.7 1.0, 2.1	19.2 12.5
	Any Insomnia Any RLS	1.8 1.5	1.2, 2.7 1.1, 2.2	19.4 20.3

Outcome	Risk Factors in Model	Relative Risk	95% CI	Attributable Risk %
Specific Phobia	Severe Insomnia	1.7	1.2, 2.5	4.4
	Moderate Insomnia	1.4	1.1, 1.8	7.1
	Any Insomnia	1.7	1.3, 2.2	14.0
	RLS Definite	1.4	1.1, 1.7	8.8
	RLS Probable	1.0	0.8, 1.4	0.5
	Any RLS	1.3	1.1, 1.7	12.9
	Severe Insomnia & RLS Definite	1.7 1.4	1.2, 2.4 1.1, 1.7	4.2 8.8
	Any Insomnia RLS Definite	1.6 1.3	1.2, 2.0 1.0, 1.6	12.9 7.6
	Any Insomnia Any RLS	1.6 1.3	1.3, 2.1 1.0, 1.6	13.3 10.8
Outcome	**Risk Factors in Model**	**Relative Risk ***	**95% CI**	**Attributable Risk %**
Any Phobia	Severe Insomnia	1.6	1.2, 2.2	3.5
	Moderate Insomnia	1.5	1.2, 1.9	8.6
	Any Insomnia	1.7	1.4, 2.1	14.6
	RLS Definite	1.3	1.0, 1.5	6.7
	RLS Probable	1.1	0.9, 1.4	1.7
	Any RLS	1.3	1.1, 1.6	11.8
	Severe Insomnia & RLS Definite	1.6 1.3	1.2, 2.2 1.0, 1.5	3.4 6.7
	Any Insomnia RLS Definite	1.7 1.2	1.3, 2.1 1.0, 1.5	14.0 5.4
	Any Insomnia Any RLS	1.7 1.2	1.3, 2.1 1.0, 1.5	14.0 9.9

Outcome	Predictors in Model	Relative Risk *	95% CI	Attributable Risk %
Drug or alcohol Abuse	Severe Insomnia	3.5	1.9, 6.8	10.9
	Moderate Insomnia	1.4	0.8, 2.5	8.4
	Any Insomnia	2.3	1.4, 3.9	25.1
	RLS Definite	1.1	0.7, 1.9	3.7
	RLS Probable	1.3	0.8, 2.2	5.5
	Any RLS	1.4	0.8, 2.2	14.4
	Severe Insomnia & RLS Definite	3.6 1.2	1.9, 6.9 0.7, 1.9	10.9 4.9
	Any Insomnia RLS Definite	2.3 1.0	1.4, 3.9 0.6, 1.7	24.9 0.9
	Any Insomnia Any RLS	2.3 1.2	1.3, 3.8 0.8, 1.9	16.0 10.2

* Controlled for gender, age, education, PCS, and ADG's
** Both insomnia and RLS simultaneously in the model.

Table 2.6 Relative Risk and Attributable Risk % for DSM-IV mental health disorders in the presence of insomnia and RLS adjusted for demographics and health status.

Insomnia is statistically associated with each of the mental health disorders listed in Table 2.6, although more strongly associated with major depression, generalized anxiety disorder, and substance abuse. The presence of insomnia doubles or triples the probability of these mental health outcomes. RLS is statistically associated with generalized anxiety disorder, panic attacks, and with specific phobia. The presence of RLS multiples the probability of these outcomes by approximately 1.5.

The calculation of attributable risk %, which is heavily influenced by the proportion of exposed cases, gives a somewhat different perspective. An exposure with a small relative risk can result in a substantial attributable risk % if a large proportion is exposed. Twenty percent or more of the cases of major depression, generalized anxiety disorder, panic attack, and substance abuse can be attributed to insomnia. In addition, 10 to 20% of generalized anxiety disorder and panic attack can be attributed to RLS.

Task 3:

Document the level of health care utilization at baseline interview and at one year follow-up associated with insomnia and RLS adjusting for comorbid health conditions.

Contributes to research goal:

- To document the level of health care utilization at baseline interview and at one year follow-up associated with insomnia and RLS adjusting for comorbid health conditions;

Because patients of the VA health care system may also use health care providers outside of the VA in addition to VA providers, we obtained data both from the VA medical record and from patient interview.

The baseline utilization data were obtained from the Time 1 questionnaires. The medical record was searched for health care utilization in the month prior to interview. This data collection is documented under TASK 1 above.

Task 3.a Conduct interviews by mail with 1914 VA clients to determine health care utilization one year after baseline interview.

The one year follow-up interviews were completed in September, 2005. A total of 1255 follow-up surveys were returned to us. Seven of these could not be matched to study participants, leaving 1248 correctly completed Time 2 interview which is a 71% response rate. Forty-two additional study members were identified as deceased before the Time 2 survey date. The deceased were excluded from the Time 2 data analysis and from analysis comparing Time 1 to Time 2.

Tables 3.1 through 3.3 show the demographic characteristics of the Time 2 respondents. The actual demographic data were collected in the Time 1 interview. In addition to the information shown, among the respondents to the Time 2 survey, 29 (2.3%) had reported at Time 1 that they were of Hispanic origin.

Task 3.b Extract time 2 utilization data from 1914 electronic medical records.

Time 2 medical record data was obtained after the one year anniversary of the study member's interview. As was done for Time 1, the medical record data covered the month prior to the one year follow-up date. In order to include prescriptions which are refilled infrequently, we obtained prescription data up to 6 months after Time 2 interview. Thus, the final prescription data was obtained in March, 2006.

Task 3.c Data entry, cleaning, and analysis

Data Analysis Methods

Study members were asked at Time 1 and Time 2 interview about their use of health services in the month prior to interview. They were also asked if the health care event occurred at a VA or non VA facility. We obtained medical record data from VAMC files for office visits, hospitalizations, inpatient and outpatient surgery, laboratory tests, radiology, and prescriptions. Prescription data was obtained only from VAMC records. Most patients fill their prescriptions through the VA pharmacy as VA drug cost are substantially lower than other pharmacies.

	Time 1: Number (%)	Time 2: Number (%)	Time 2 Response Rate (%)
Males			
Age < 41	85 (4.8)	31 (2.5)	36
Age 41-50	184 (10.4)	95 (7.6)	52
Age 51-60	282 (16.0)	203 (16.3)	72
Age 61-70	252 (14.3)	201 (16.1)	80
Age 71-80	298 (16.9)	225 (18.0)	76
Age > 80	311 (17.7)	262 (21.0)	84
Females			
Age < 51	185 (10.5)	103 (8.3)	56
Age > 50	164 (9.3)	128 (10.3)	78
Total	1761 (100.0)	1248 (100.0)	71

Table 3.1. Age and gender distribution of respondents and response rate to Time 2 survey in comparison to Time 1.

Primary Race/ Ethnicity	Time 1: Number (%)	Time 2: Number*	Time 2 Response Rate (%)
American Indian or Alaskan Native	14 (0.7)	10	71
Asian	5 (0.3)	3	60
Black or African American	144 (8.1)	63	44
White or Caucasian	1565 (88.9)	1119	72
Declined to respond	7 (0.4)		
No response	26 (1.5)		
Total	1761		

* Persons who responded to Time 2 interview as characterized at Time 1.

Table 3.2. Distribution of Time 2 respondents by race in comparison to Time 1 .

Secondary Race / Ethnicity	Time 1: Number	Time 2: Number*	Time 2 Response Rate (%)
American Indian or Alaskan Native	46 (2.6)	31	67
Asian	2 (0.1)	2	100
Black or African American	4 (0.2)	1	25
White or Caucasian	4 (0.2)	3	75
None reported	1705 (96.8)		

* Persons who responded to Time 2 interview characterized at Time 1.

Table 3.3. Distribution and response rate of study members by second reported race in comparison to Time 1 .

We consider the VA medical record to be the most accurate record of health care utilization. Because study members may also receive care from outside physicians, reported health care provided by non-VA sources was combined with VA care. If a study member reported a visit to a physician, a diagnostic test, a hospitalization, or an outpatient surgical procedure outside of the VA system, this was added to utilization determined from the VA medical record. By combining this information, we hope to develop a more complete picture of the health care utilization of study members.

We conducted analysis to model numbers of primary care and specialty care visits, numbers of combined diagnostic procedures (labs, radiology and other procedures), numbers of prescriptions, and numbers of hospital days. Using each of the above variables as the dependent variable in least squares regression modeling, we examined the effect of insomnia and /or RLS after controlling for gender, age, race/ethnicity, education, ADG's, PCS and MCS. All variables were entered into the regression model and the model was subsequently simplified using statistical significance of the independent variable and the adjusted R^2 of the model as the criteria. This analysis was conducted for the Time 1 utilization data.

For the Time 2 data, although not all study members had returned the Time 2 survey, because medical record data was available for all study members, all were included in the analysis. The exception is 42 study members who died between Time 1 and Time 2. Five of those died within one month of their Time 2 interview date and thus had eligible medical record data. All of the deceased were excluded from Time 2 data analysis because intensive resource utilization around the time of death could bias the results of the analysis.

The Time 2 data allows us to carry out a prospective analysis of utilization. Using this data, we can address questions about the effect of insomnia or RLS on utilization prospectively after adjusting for baseline utilization at Time 1. Specifically, we designed analysis to address the null hypothesis: the change in resource utilization from Time 1 to Time 2 is the same in persons with and with out insomnia and /or RLS. The alternative hypothesis is that persons with RLS or insomnia show an increase in resource utilization relative to those without insomnia and /or RLS.

Results

Table 3.4 shows several categories of utilization at Time 1 and Time 2 for the entire sample and stratified by gender. There is an apparently larger number of primary care visits reported at Time 1 because the data include the primary care visit at which each study member was recruited. Tables A.14.a and b in Appendix A show this data in more detail. Table A14.c and d gives the same information for Time 2.

As these data are for a one month period, there are few hospitalizations. Female patients also reported 4 same day and 10 inpatient surgical procedures. Males reported 18 same day surgeries and 58 inpatient surgeries. We found a total of 4 surgical procedures (1 female, 3 males) in the medical record. We speculate that the discrepancy results from a combination of patient over reporting and use of physicians outside the VA.

	Women			Men			All		
	Mean	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Number of Primary Care Physician Visits (medical record and interview)									
Time 1	1.32	0.96	349	1.29	0.72	1412	1.30	0.77	1761
Time 2	0.78	1.30	344	0.73	0.96	1375	0.74	1.04	1719
Number of Visits to Specialist Physicians (medical record and interview)									
Time 1	0.26	0.89	349	0.35	0.78	1412	0.33	0.8	1761
Time 2	0.89	1.50	343	0.71	1.36	1375	0.75	1.39	1718
Number of Prescriptions (all Rx 2 months prior and 1 month after interview)									
Time 1	7.02	8.46	348	6.78	6.13	1412	6.98	6.66	1761
Time 2	6.48	6.70	343	6.18	6.22	1375	6.24	6.31	1719
Number of Diagnostic Procedures (Medical Records and Interview - includes radiology)									
Time 1	0.58	1.08	349	0.59	0.97	1412	0.59	0.99	1761
Time 2	0.38	0.89	344	0.39	1.01	1375	0.39	0.99	1719
Hospitalizations LOS (VA and not -VA)									
Time 1	0.13	1.03	349	0.15	1.74	1412	0.14	1.62	1761
Time 2	0.03	0.29	344	0.15	1.27	1375	0.13	1.15	1719

Table 3.4 Use of health care services at Time 1 and Time 2.

We used least squares regression to model primary care and specialty care visits, diagnostic procedures (including labs, radiology, and other procedures, e.g. pulmonary function testing), and prescription medications. The visit and procedures data include reports from study members of utilization outside of the VA. Prescription information comes only from the VA system.

Table 3.5 shows the results of modeling the Time 1 utilization data. The PCS of the VA SF-36 was related to each of the utilization measures. The negative sign of the coefficient indicates that as

physical health deteriorates, health care utilization increases. The MCS was associated only with prescription medication use. Neither insomnia or RLS was associated with numbers of primary care or specialty care office visits.

RLS was associated with the number of prescription medications. However, the direction of the association is the opposite of expected – persons with definite RLS used fewer medications. This result is surprising, and as the analysis controlled for demographic factors and health status, it is not due to confounding by those factors. Additional data analysis will be required to understand this finding. Insomnia was positively associated with diagnostic procedures even after controlling for physical and mental health status. RLS showed no association with diagnostic procedures.

Dependent Variable		Effect of			Adjusted for
	Adjusted R^2	Variable	Coefficient	P value	
Primary Care Visits	0.07	PCS	-0.00749	0.0001	Age group, race categories, selected ADG's
		MCS	0.00114	0.54	
		Insomnia score	-0.00486	0.09	
		RLS Def (0/1)	.02024	0.65	
Specialty Care Visits	0.08	PCS	-0.00973	<0.0001	Age group, education, selected ADG's
		MCS	-0.00092	0.67	
		Insomnia (Sev 0/1)	0.15847	0.15	
		RLS Def (0/1)	0.08563	0.07	
Prescription Medications	0.30	PCS	-0.01742	<0.001	Age, gender, education, selected ADG's
		MCS	-0.00965	<0.001	
		Insomnia score	0.00379	0.27	
		RLS definite (0/1)	-0.14498	0.002	
Diagnostic procedures	0.04	PCS	-0.0052	0.02	Age group, white race, African American race, education, selected ADG's
		MCS	-0.00338	0.18	
		Insomnia (Sev 0/1)	0.59994	<0.0001	
		RLS (Def)/1)	0.03646	0.54	

Table 3.5 Results of least squares regression modeling of health care utilization.

Table 3.6 shows the prospective analysis of the change in health care utilization from Time 1 to Time 2. In this analysis, the dependent variable is the difference between the level of utilization at Time 1 and Time 2. We hypothesized that persons who reported insomnia or RLS at Time 1 would show increased utilization at Time 2. The analysis was controlled for demographic factors, ADG's, and the VA SF-36 MCS and PCS.

As hypothesized, persons who reported insomnia at Time 1 had increased numbers of specialty care visits, diagnostic procedures, and prescription medications at Time 2. However, persons who reported insomnia at Time 1 had fewer primary care visits at Time 2. RLS was not associated with a change in any type of health care utilization.

Plans for future analysis of levels of health care utilization include the use of empirical cost estimates for different types of utilization. Two methods of costing outpatient utilization within the VA system have been discussed by Phibbs and Schmitt.(13) These or a similar approach will be used to weight different types of utilization. This will allow us to combine types of utilization into a more accurate summary measure.

Dependent Variable		Effect of			Adjusted for
Difference Time 1 – Time 2*					
	Adjusted R^2	Variable	Coefficient	P value	
Primary Care Visits	0.02	PCS	0.00513	0.06	Age group, race categories, selected ADG's
		MCS	0.00187	0.56	
		Insomnia score	0.15341	0.02	
		RLS (none/ prob/ def)	0.03469	0.60	
Specialty Care Visits	0.04	PCS	0.00201	0.63	Age group, gender, race, selected ADG's
		MCS	0.00201	0.68	
		Insomnia (none/ mod severe)	-0.29567	0.005	
		RLS definite (0/1)	0.08696	0.41	
Prescription medications	0.02	PCS	0.01546	0.20	Age, gender, education, selected ADG's
		MCS	0.01223	0.38	
		Insomnia (Sev 0/1)	-1.76945	0.02	
		RLS (none / prob / def)	0.02314	0.88	
Diagnostic procedures	0.03	PCS	0.00364	0.19	Age group, race, education, selected ADG's
		MCS	0.00290	0.33	
		Insomnia (severe 0/1)	-0.64472	<0.0001	
		RLS (none / Prob / def)	-0.01214	0.52	
* Smaller values of difference mean increased utilization at Time 2.					

Table 3.6 Results of least squares regression modeling of the change in health care utilization from Time 1 to Time 2.

Task 4.

*A*ssess the validity of the RLS questionnaire using interview by a trained clinician as the gold standard.

Contributes to research goal:
*A*ssess the validity of the RLS questionnaire using interview by a trained clinician as the gold standard.

Task 4.a Recruit study members who are patients at the Akron CBOC and conduct clinical assessment.
Task 4.b Analyze data
Task 4.c Manuscript preparation

The task is complete. A manuscript has been submitted to the journal, *Sleep Medicine.* A copy of the manuscript is attached in Appendix C.

Introduction.

The purpose of Task 4 is to assess the test characteristics of the Johns Hopkins Telephone Diagnostic Interview (TDI). This interview was used in the overall study to identify persons who have a high probability of being RLS cases. The assessment of the accuracy and repeatability of the TDI is of interest to the larger scientific community, as the interview may be used in other epidemiologic studies of RLS. In the context of our study of the prevalence and outcomes of RLS among veterans, the values of sensitivity and specificity of the TDI will be used to adjust the prevalence values which will be reported elsewhere in this project.

Methods.

Patients who were participants in the main study and who obtain their primary care at the Akron CBOC were recruited into the Validation Substudy. For the Validation interview, the insomnia severity scale and the RLS questionnaire were administered by a registered nurse. Patients then meet with Dr. Margaret Panzner for a clinical interview. If a study member reported symptoms of RLS, Dr. Panzner made a clinical determination about RLS case status or determined that the symptoms result from an RLS mimic. For patients who were judged to be cases, Dr. Panzner classified the disease as primary or secondary to some other health condition.

The data analysis plan included: 1) calculation of the sensitivity and specificity of the Time 1 interview and the Validation interview using the clinical interview as the gold standard for both comparisons; calculation of the associated 95% confidence intervals; and 3) calculation of the test-retest reliability of the RLS instrument from Time 1 to Validation interview using the Kappa statistic.

Results

Our sample size goal for this substudy was to obtain complete study protocol on 82 study members. Eight-five study members completed the completed the Validation 2 interview and 74 study members completed the entire protocol. In May, 2006, the rate of addition of study members with completed protocols dropped to below one per month, and we made a decision to end patient recruitment and complete the data analysis.

Table 4.1 shows the demographic characteristics of the final sample.

	Completed Validation TDI Interview			Completed TDI and Clinical Interview.		
	No.	%	% of Selected	No.	%	% of Selected
Total	85	100	39	74	100	34
Gender						
Male	75	88	38	65	88	33
Female	10	12	53	9	12	47
Age						
18 - 29	2	2	50	0	0	0
30 - 39	4	5	50	4	5	50
40 - 49	8	9	31	5	7	19
50 - 59	21	25	46	20	27	43
60 – 69	19	22	40	18	24	38
70 – 79	13	15	37	12	16	34
= > 80	18	21	35	15	20	29

Table 4.1. Demographic Characteristics of Patients Selected for the Study and of Study

We considered several alternative configurations of RLS symptoms in order to determine empirically the most accurate use of the questionnaire. The results of several of the alternatives that we considered are shown in Table 4.2.

Based on this analysis, we have chosen to use a rule requiring 3 or 4 symptoms with no additional requirement for symptoms frequency for the remainder of the study. This rule obtains a sensitivity = 63% and a specificity = 88%. This rule provides the definition for probable (3 symptoms) and definite (4 symptoms) used elsewhere in this report.

An alternative rule which obtain a higher accuracy was also developed and will be presented in our publication for confirmation by other investigators.

	Number of symptoms	Sensitivity	95% CI Upper	95% CI Lower	Specificity	95% CI Upper	95% CI Lower
Validation Interview							
Exclude Automatic only*							
	4	0.56	0.73	0.39	0.81	0.93	0.69
	3 or 4	0.75	0.88	0.62	0.71	0.86	0.56
Exclude Automatic & Symptom Days < 2/ month							
	4	0.56	0.73	0.39	0.83	0.94	0.72
	3 or 4	0.73	0.87	0.59	0.74	0.89	0.59
Time 1 Interview							
Exclude Automatic only							
	4	0.44	0.61	0.27	0.83	0.94	0.72
	3 or 4	0.63	0.78	0.48	0.88	0.99	0.77
Exclude Automatic & Symptoms Days < 2/month							
	4	0.41	0.58	0.24	0.86	0.96	0.76
	3 or 4	0.55	0.70	0.40	0.88	0.99	0.77

*Note : Automatic exclusions are: if the respondent denied BOTH (urge to move and leg feeling) or (said the feelings were ALWAYS cramps).

Alternate Rule**	Sensitivity	95% CI Upper	95% CI Lower	Specificity	95% CI Upper	95% CI Lower
Time 2 Interview						
Exclude Cramp only	0.75	0.88	0.62	0.71	0.86	0.56
Exclude if Days <2 or Cramp	0.73	0.87	0.59	0.74	0.89	0.59
Time 1 Interview						
Exclude Cramp only	0.75	0.88	0.62	0.74	0.89	0.59
Exclude if Days <2 or Cramp	0.68	0.82	0.54	0.82	0.95	0.69

**Considered to be a case if uncomfortable leg feeling or urge to move and relief with walking = yes (2 symptoms). Also a case if there are 3 symptoms and relief with walking is negative.

Table 4.2 Empirical accuracy of several rules for RLS identification.

Task 5.

Assess the external validity of the Sleep Study sample with respect to the population of VA patients who have had a visit in the past year.

Contributes to research goal:

- To estimate the prevalence of Restless Legs Syndrome and insomnia.

Task 5.a Extract population data from electronic patient record system
Task 5.b Data analysis

These two tasks are complete.

Method.

We obtained datasets which contained a record for each primary care visit and for each new prescription for each patient who received outpatient care at the Cleveland VAMC for the fiscal year, October 1, 2003 to September 30, 2004. The data included: date of each primary care visit; date of each new prescription; and the drug class code. These data were merged with a dataset which contained patient age and gender. The data of participants in our RLS research was identified. This dataset was used for all of the analysis reported for Task 5.

Results

We compared: the age and gender distribution of the VA Sleep Study participants to all patients obtaining care at the Cleveland VAMC (Table 5.1) ; and compared the mean number of primary care visits (Table 5.2) and mean number of new prescriptions (Table 5.3) for the two patient groups. We also show the frequency distributions of number of primary care visits (Figure 5.1) and number of new prescriptions (Figure 5.2) for the two patient groups.

We do not present statistical tests for the data evaluated in this Task. Because of the extremely large sample size for the Cleveland VAMC Outpatient arm of the comparison, any statistical test is expected to find a statistically significant difference. Therefore, conclusions based on such tests would be meaningless.

		Cleveland VA Outpatient care		Sleep Study participants	
Males		Number	Percent	Number	Percent
Age Group	20's	515	0.8	16	1.1
	30's	1431	2.3	50	3.6
	40's	4082	6.6	154	11.0
	50's	12843	20.6	273	19.5
	60's	12263	19.7	250	17.9
	70's	19609	31.5	286	20.4
	80's	11556	18.6	370	26.5
	Total	62299	100.0	1399	100.0
Females					
Age Group	20's	191	8.2	25	7.3
	30's	348	15.0	42	12.2
	40's	594	25.5	101	29.5
	50's	516	22.2	79	23.0
	60's	204	8.8	40	11.7
	70's	136	5.8	16	4.7
	80's	338	14.5	40	11.7
	Total	2327	100.0	343	100.0

Table 5.1. Comparison of gender-age distribution of study members to Cleveland VAMC outpatient population, fiscal year, October, 2003 to September, 2004.

Gender	Age Group	Patients in Sleep Study Mean n. visits (s.d., n)	Cleveland VAMC population Mean n. visits (s.d., n)
Females	20	4.64 (2.84, 25)	2.90 (3.03, 191)
	30	3.71 (2.58, 42)	3.03 (2.84, 348)
	40	5.73 (4.14, 101)	3.39 (2.86, 594)
	50	5.23 (3.65, 79)	3.79 (2.90, 516)
	60	4.03 (2.52, 40)	3.99 (3.24, 204)
	70	3.38 (1.82, 16)	3.38 (3.04, 136)
	80	4.48 (3.49, 40)	2.99 (2.31, 338)
	Total	4.83 (3.52, 343)	3.38 (2.87, 2327)
Males	20	3.00 (2.39, 16)	2.02 (1.57, 515)
	30	3.14 (2.11, 50)	2.30 (1.94, 1431)
	40	4.01 (3.02, 154)	2.79 (2.31, 4082)
	50	4.73 (6.60, 273)	3.38 (2.88, 12843)
	60	4.30 (3.48, 250)	3.40 (2.79, 12263)
	70	3.93 (3.43, 286)	3.17 (2.50, 19609)
	80	3.72 (2.83, 370)	3.23 (2.55, 11556)
	Total	4.06 (4.07, 1399)	3.21 (2.63, 62299)

Table 5.2. Mean number of primary care visits (unadjusted) stratified by gender and age.

Gender	Age Group	Patients in Sleep Study Mean n. Rx. (s.d., n)	Cleveland VAMC population Mean n. Rx. (s.d., n)
Females	20	7.36 (6.78, 25)	5.17 (6.69, 191)
	30	11.98 (10.31, 42)	8.18 (9.03, 348)
	40	20.71 (21.02, 101)	14.76 (17.56, 594)
	50	19.06 (16.60, 79)	17.47 (18.70, 516)
	60	16.88 (10.24, 40)	16.68 (17.22, 204)
	70	13.13 (10.83, 16)	14.93 (15.04, 136)
	80	13.65 (9.81, 40)	12.11 (10.98, 338)
	Total	16.66 (15.90, 343)	13.38 (15.60, 2327)
Males	20	4.63 (5.15, 16)	3.89 (5.73, 515)
	30	7.02 (7.91, 50)	6.65 (9.63, 1431)
	40	14.85 (14.24, 154)	12.30 (15.49, 4082)
	50	17.04 (15.06, 273)	14.31 (14.98, 12843)
	60	14.64 (12.49, 250)	12.65 (12.92, 12263)
	70	12.52 (8.62, 286)	11.59 (10.26, 19609)
	80	11.63 (8.49, 370)	11.50 (9.52, 11556)
	Total	13.52 (11.71, 1399)	12.21 (12.23, 62299)

Table 5.3. Mean number of new prescriptions stratified by gender and age.

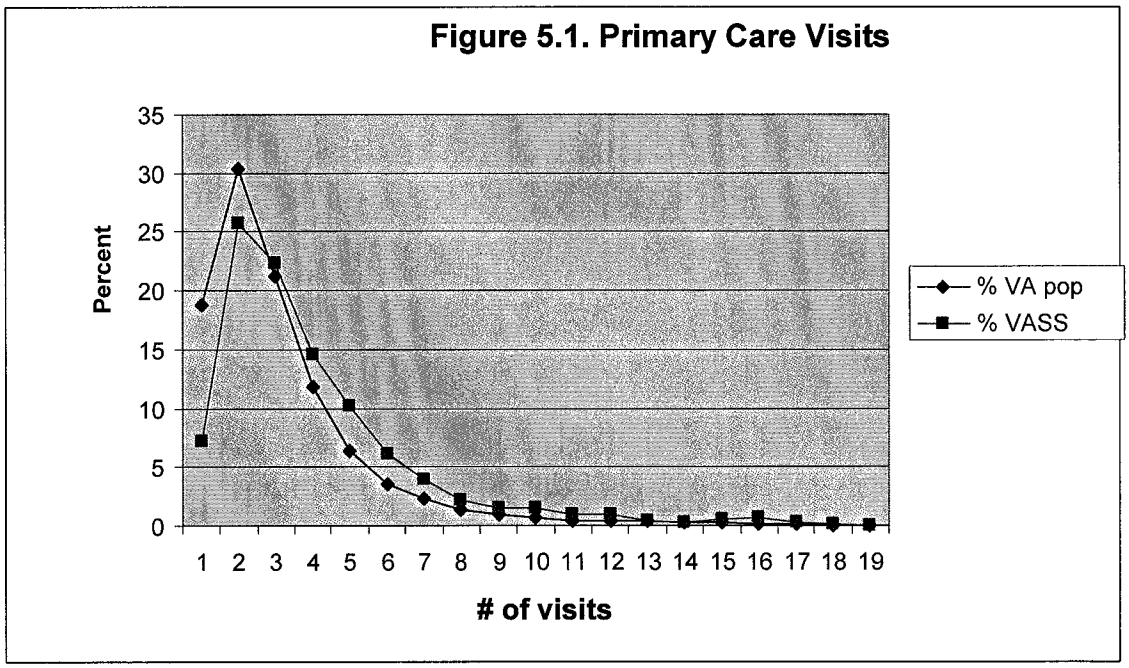
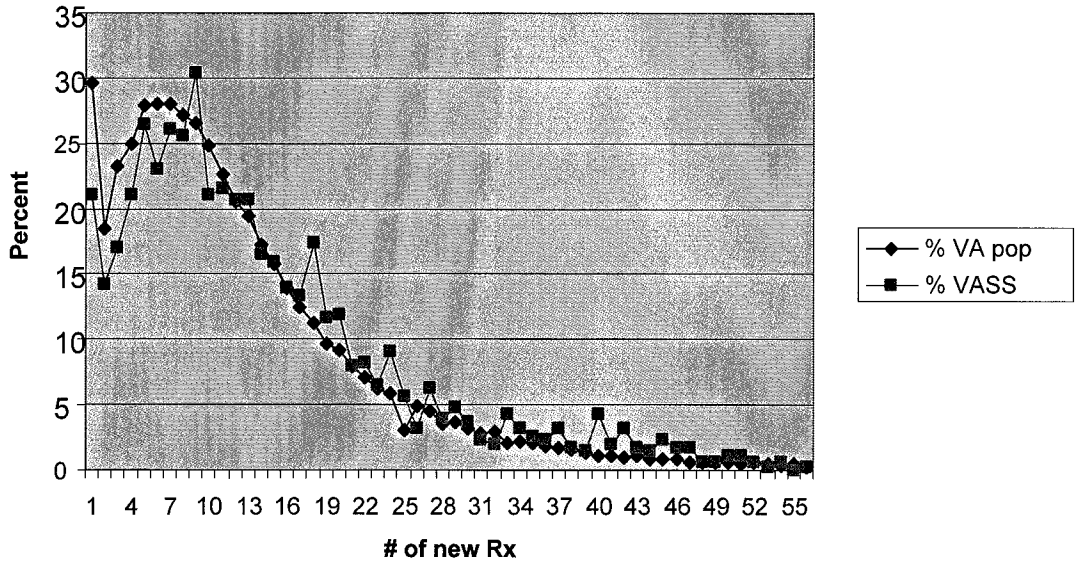


Figure 5.2. Number of New Prescriptions



The gender- age distributions of the Veterans Sleep study sample and the Cleveland VAMC outpatient population are only roughly similar. We did not expect the gender-age distribution of the sample to exactly represent the population. The differences result from the sampling scheme for the Sleep Study sample which was designed to obtain precise estimates of RLS and insomnia prevalence in gender-age strata rather than to directly represent the demographics of the background population.

Tables 5.2 and 5.3 suggest that the participant in the VA Sleep Study are somewhat sicker than the background population. Sleep Study participants had 0.95 more office visits (4.17 visits versus 3.22 visits) and 1.74 more new prescriptions (13.99 versus 12.25) than the overall population. This is expected because the study members were recruited at the time of a primary care visit. Using this sampling scheme, persons who make more office visits have a higher probability of being sampled. Lee and colleagues documented the effect of this sampling approach in a VA sample and concluded that that such a sample represents the subgroup of patients who have 4 or more office visits of any type during a year.(14) These authors found that patients selected at a primary care office visit had 0.8 more primary care visits in a year. We plan additional analysis following the model of Lee and colleagues to determine to what extent their conclusions apply to the Sleep Study sample or alternatively, what subgroup of the VA population is represented by the Sleep Study sample.

Figures 5.1 and 5.2 indicate that the utilization characteristics of the Sleep Study sample, like the background population, are skewed to the right. The overall frequency distributions of the study sample are shifted to the right of the background population.

Task 5.c **Manuscript preparation.** This information will be incorporated in the manuscript in preparation for *Task 1.* The paper by Lee and colleagues contains an important discussion of the utility of such visit based samples. Points from their discussion will be included in the

discussion of the external validity and conclusions which can be drawn from the sample included in this research.

Task 6

Conduct a pilot study of an aerobic exercise intervention to improve sleep quality among RLS patients by moderating their RLS symptoms.

Identify RLS cases, confirm diagnosis and recruit up to 30 study members. Hire and train staff. (Months 25 – 27)
Compliance trial. (Month 28)
Conduct 3 month crossover study. 3 month intervention and 3 month control condition. (Month 29-34)
Analyze data and prepare report. (Month 35-36)

Human Subject approval of the project by the Department of Defense IRB was received in July, 2005. At that time, hiring and training personnel started.

The study protocol called for two arms of the study, one carried out through the Community Based Outpatient Center (CBOC) located in Akron, Ohio and one through the CBOC located in Youngstown, Ohio. Eligible study members must be definite or probable RLS cases, and meet a series of other eligibility criteria, including current insomnia complaints, and permission from their primary care physician for participation.

Arrangements were made with the Akron and Youngstown CBOC's for patient recruiting and a residents physician from St Elizabeth's Hospital in Youngstown, OH was enlisted to assist with patient intake interviews. Arrangements were made to run the exercise arm of the study at the Firestone YMCA in Akron and at the Jewish Community Center in Youngstown.

The following is a synopsis of our attempts to recruit participants for this study.

Akron/Canton (December, 2005)

Sent 47 recruitment letters and tried to reach all 47 by telephone.
- 13 planned to attend meeting
- 3 were too busy
- 1 was too ill
- 1 said Akron clinic was too far to travel
- 1 had no ride to meeting
- 9 not interested
- 2 refused without any reason given
- 5 unable to reach by phone
- 12 left multiple messages but received no response

6 attended the meeting.
- All 6 were enrolled. 4 had medical problems and were excluded.

Sent 24 letters for next meeting.
- No one showed up for the meeting

Youngstown/Warren(March, 2006)

Sent 53 recruitment letters and tried to reach all 53 by telephone.

13 planned to attend meeting
4 were too busy
4 not interested
1 too far to travel to clinic
7 refused without any reason given
4 unable to reach
20 multiple messages but received no response

5 attended meeting
2 enrolled
1 had no ride to fitness center, not enough money for gas
1 was too busy
1 didn't have any RLS symptoms

32 sent letter for next meeting
1 new person showed up and enrolled—this person later dropped out because the person didn't think that the symptoms were related to RLS

Of the 2 that we enrolled, only 1 continued to come to meetings.

Result

Because of our inability to recruit study members, the protocol was terminated after discussion with the assigned project officer.

A single study member completed the 12 week exercise arm of the study. This study member completed all of the requirements of the intervention including daily sleep diary, wearing the actigraph during sleep, and attending the twice weekly exercise sessions. An exit interview was conducted at which the study member reported that sleep was not disturbed by wearing the actigraph. The exercise leader reported that the study member successfully increased exercise tolerance over the course of the intervention. All study equipment (actigraph, heart rate monitor, and blood pressure monitors) functioned as expected.

Discussion

Aukerman and colleagues recently reported a small trial of an exercise intervention for RLS symptoms. (15) From television ads, notices in local newspapers, and fliers in physicians offices, they received inquiries from 200 persons and were able to enroll 41 study members. Because Aukerman and colleagues were more successful at recruiting study members, we have speculated about the difference between our potential study members and recruiting procedure and theirs. The study members of Aukerman were self selected and were likely quite symptomatic. In contrast, our potential study members were selected by us. Although they were chosen to meet the criteria for RLS, few of them were very symptomatic. Thus, they were less motivated to participate in an activity that might mitigate their symptoms. In addition, a characteristic of the VA health care system is that patients are in often in poor health and have limited financial resources. This may have made them less likely to participate in an activity that might strain their resources with little perceived benefit to themselves.

In conclusion, we gained some insight into the type of patient to target in any future research efforts on this topic. Specifically, any proposed exercise intervention for RLS symptoms should be directed to persons who are sufficiently discomforted by their symptoms to be motivated to participate.

KEY RESEARCH ACCOMPLISHMENTS

- Recruited and interviewed 1761 study members.
- Extracted Time 1 and Time 2 medical record data for 1761 study members.
- Obtained additional office visit data going back 18 months for all study members for case-mix adjustment.
- Operationalized approaches to case mix adjustment.
- Mailed 1761 follow-up questionnaires; obtained 71% response to follow-up survey.
- Cleaned Time 1 and Time 2 patient interview datasets and prepared working data files.
- Cleaned Time 1 and Time 2 medical record datasets and prepared working data files.
- Obtained utilization data on background population and demonstrated comparability of study sample to background population.
- Conducted Validation Substudy to assess accuracy of Johns Hopkins Telephone Diagnostic Instrument for RLS.
- Developed rule to define RLS case status based on Validation Substudy analysis.
- Conducted two rounds of recruiting for study members for exercise intervention study.
- Completed exercise protocol with one study member.
- Completed data analysis of data collected at Time 1 interview.
  - Description of study participants.
  - Estimates of the prevalence of RLS, insomnia, daytime sleepiness, and mental health status.
  - Estimates of insomnia and RLS cases with a corresponding diagnosis in the VA medical record.
  - Estimates of the relative risk and attributable risk % of insomnia and day sleepiness associated with RLS.
  - Comparison of the SF-36 profiles of study members to published national comparison samples.
  - Estimates of the relationship between insomnia and / or RLS and VA SF-36 composite scores.
  - Relationship between VA SF-36 scores and WHO CIDI scores.
  - Estimates of the relative risk and attributable risk % of mental health conditions associated with insomnia and / or RLS controlled for health status.
- Completed data analysis of health care utilization data from interview and medical record.
  - Description of health care utilization (primary care and specialty care visits, diagnostic procedures, prescription medications, and hospitalizations) and Time 1 and Time 2.
  - Estimate relationship of insomnia and /or RLS with health care utilization at Time 1 after adjusting for health status.
  - Estimate relationship of insomnia and /or RLS with the change in health care utilization from Time 1 to Time 2 after adjusting for health status.

REPORTABLE OUTCOMES

Posters presented at scientific meetings.

1. Poster presented at the meeting of the Associated Professional Sleep Societies (APSS) meeting, Denver, June, 2005. Related abstract published in a special issue of the Journal, *Sleep* 2005; 26:A276.

2. Paper presented at the annual meeting of the Society for Epidemiologic Research, Toronto, Ontario, Canada, June, 2005. Related abstract published in a special issue of *the American Journal of Epidemiology* 2005; 161(S1):A90.

3. Poster presented at the Case Western Reserve University Research Showcase; April, 2005; Cleveland, OH. Ober SK, Bourguet CC, and Baughman KR. Insomnia and Daytime Sleepiness: Risk attributable to RLS, BMI, smoking, and alcohol in a VA outpatient population.

4. Poster presented at the annual meeting of Associated Professional Sleep Societies, Minneapolis, MN, June, 2007. Accuracy and Reproducibility of the Johns Hopkins Telephone Diagnostic Instrument for Restless Legs Syndrome. Claire C. Bourguet, Ph.D., Scott K. Ober, MD, MBA, Richard P. Steiner, Ph.D., Kristin R. Baughman, Ph.D., Margaret P. Panzner, MD

5. Poster presented at the annual meeting of Associated Professional Sleep Societies, Minneapolis, MN, June, 2007. The Association of Antidepressant Use with Restless Legs Syndrome in a VA Outpatient Population. Baughman KB, Bourguet CC, Ober SK, Steiner RP

Employment
Kristin R. Baughman, Ph.D. who was the Project Coordinator of this project was offered and has accepted a tenure track position as an Assistant Professor of Community Health Sciences at NEOUCOM.

Manuscript submitted
Reproducibility and Accuracy of the Johns Hopkins Telephone Diagnostic Interview for Restless Legs Syndrome. Claire C. Bourguet, Scott K. Ober, Margaret P. Panzner, Kristin R. Baughman, Richard P. Steiner. Submitted to *Sleep Medicine* in August, 2007.

CONCLUSIONS

Using number of primary care visits and new prescriptions as a criteria, the participants in the Veterans Sleep Study are comparable to a subgroup of Veterans who have more than one office visit each year. In a comparison of VA SF-36 profiles, the Sleep Study participants show an overall health related quality of life profile that is slightly better than the participants in the Veterans Health Study. Participants in the Veterans Sleep Study report mental health status that is similar to the National Survey of Functional Health, although they report poorer physical health status.

Using expert clinical interview as the gold standard, the Johns Hopkins Restless Legs Syndrome Telephone Diagnostic Interview has a 63% sensitivity (95% CI: 48%, 78%) and 88% specificity (95% CI: 77%, 99%). Reproducibility was acceptable (kappa = 0.55, $p < 0.05$) for interviews that were repeated within one year, but lower (kappa = 0.34) when the interval was longer. The sensitivity and specificity found in this study are lower than have previously been reported in the literature.

The Johns Hopkins TDI is currently the only diagnostic instrument for RLS for which validation data have been published. The previously published data apply to narrowly defined clinical specialty samples. Our data suggest that the TDI is less accurate in primary care samples and among persons with milder RLS symptoms. In order to conduct epidemiological research on RLS, an accurate questionnaire is required. We conclude that additional questionnaire development efforts are necessary.

An attempt to enroll participants of the main study in an exercise intervention to examine hypotheses about the effect of exercise on RLS symptoms failed. We speculate the our inability to interest study members in the intervention trial resulted from the relatively mild quality of their symptoms. We speculate that persons whose symptoms are more severe and troubling to their quality of life would be more likely to enroll. Thus, we recommend that any further efforts to examine a hypothesis about the effect of exercise on RLS symptoms be examined among persons who are severely symptomatic. This should be at a minimum, persons who report symptoms most days of the week.

The levels of RLS, insomnia, and daytime sleepiness are high in this group of VA outpatients. Thirty-seven percent of respondents reported 3 or more RLS symptoms and 22% met all 4 IRLSSG criteria for RLS. Thirteen percent reported moderate insomnia and 3% reported severe insomnia. Seven percent reported severe daytime sleepiness. While about 30% of those with reported insomnia had a sleep diagnosis in their medical record, fewer than 5% of those with RLS had a diagnosis in their medical record.

Estimates of the proportion of insomnia which is attributable to RLS after controlling for co-morbid health conditions indicate that approximately 20% of the insomnia observed in this group of veterans is attributable to RLS. Because RLS is virtually untreated in this population, this result suggests that the burden of insomnia could be reduced by 20% with effective treatment of RLS.

DSM-IV qualified mental health conditions are also common in this population. The prevalence values are the following: major depression, 20%; generalized anxiety disorder, 12%; specific phobias, 14%; social phobia, 6%; agoraphobia, 4%; panic attacks, 6%; alcohol dependence, 3%; drug dependence, 1%. In the presence of insomnia, the probability of depression,

generalized anxiety disorder, panic attacks, and drug or alcohol abuse are at least doubled. The risk of phobia disorders is also increased in the presence of insomnia by 60% to 70% RLS shows an association with generalized anxiety disorder and panic attack, increasing the risk of those disorders by approximately 50%.

The analysis of the relationship between the sleep disorders and mental health outcomes is cross-sectional. The means that it is strictly impossible to determine the direction of causality. However, for our analysis, we made the assumption that the direction of causality leads from sleep disorders to mental health disturbance. This allowed us to calculate the attributable risk % associated with sleep disorders for each mental health outcome. Because of the large proportion of the study sample who report a sleep disorder the resulting attributable risks are substantial. Twenty-three percent of major depression is associated with insomnia, as is 36% of generalized anxiety disorder, 19% of panic attacks, 13% of specific phobias, 14% of combined social and agoraphobia phobia, and 16% of drug or alcohol abuse. In addition, 20% of generalized anxiety disorder and 20% of panic attack disorder are attributable to RLS.

We were able to examine the effect of insomnia and RLS on health care utilization, including primary and specialty care visits, diagnostic procedures and prescription drug use, both cross-sectionally and prospectively. In the cross-sectional analysis, the most important predictor of health care utilization was the health status of the patient as measured by the PCS of the VA SF-36 and by ambulatory diagnostic groups. In addition, mental health status as measured by the MCS of the VA SF-36 was related to prescription drug use, and severe insomnia was related to an increase in number of diagnostic procedures.

The prospective analysis, in which we examined the change in health care utilization at a one year time interval, are most informative. In this analysis, we used health status data collected at Time 1 to predict the change in utilization from Time 1 to Time 2. Physical and mental health status were unrelated to changes in health care utilization. Insomnia was related to a decrease in primary care visits, along with an increase in specialty care visits, in prescription medication use, and in diagnostic procedures. After controlling for insomnia, RLS was unrelated to the change in health care utilization.

Summary

The VA outpatients who participated in the Veterans Sleep Study are representative of patients who have more than one office visit a year at the Stokes Cleveland VAMC. Thus, the results of this research can be generalized, at a minimum, to this regional health care system and, perhaps, to the VA system at large. The prevalence of insomnia, RLS, and mental health disorders in this population is substantial, and the association between sleep disorders and mental health status is clear. In combination with the documented low level of diagnosis of both insomnia and RLS, the implications for intervention are clear. In addition to possible improvements in the quality of life of the affected patients, the data suggest that treatment of insomnia may result in reduced health care utilization and subsequently reduced health care costs.

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APPENDICES

A. Detailed tables

B. Abstracts of papers and posters presented at scientific meetings.

C. Manuscript submitted to Sleep Medicine.

D. Bibliography of published abstracts

E. Presentations made at NEOUCOM

F. Personnel receiving salary support

Appendix A Detailed Tables

Table A.1: Demographic Characteristics of Sleep Study Sample.

Table A.2 Prevalence of definite or probable RLS stratified by age and gender, and corrected for the accuracy of the Johns HopkIns Telephone diagnostic Instrument.

Table A.3 Prevalence of definite RLS stratified by age and gender, and corrected for the accuracy of the Johns Hopkins Telephone Diagnostic Instrument.

Table A.4 Prevalence of Insomnia and day time sleepiness by age and gender.

Table A.5. Portion of Sleep Study members meeting CIDI criteria for the DSM-IV diagnosis of mental health and substance disorders, stratified by gender and age.

Table A.6 Conditions capable of causing RLS symptoms (secondary RLS) from medical record and patient report.

Table A.7 Diagnosis of RLS at the VA (either on the current problems list or diagnosed in the past but no longer on problems list)

Table A.8. Persons ever diagnosed with a sleep problem at the VA stratified by Insomnia Severity Scale scores

Table A.9. Persons ever diagnosed with a sleep problem at the VA stratified by Epworth Sleepiness Scale scores

Table A.10 Frequency distribution of ambulatory diagnostic groups (ADG's) by gender and age.

Table A.11 Scores on the Veterans SF36 scale stratified by age and gender.

Table A.12.a Spearman Correlations between probability of DSM-IV diagnosis assigned by CIDI score and SF36 mental health scales.

Table A.12.b Spearman Correlations between probability of DSM-IV diagnosis assigned by CIDI score and SF36 physical health scales.

Table A.13 Percent of insomnia among study members which can be attributed to RLS (population attributable fraction) using unadjusted or adjusted RLS prevalence estimates and two methods of PAR calculation.

Table A.14.a Medical Record Report of Utilization by Age and Gender Time 1.

Table A.14.b Medical Record Report of Utilization by Ethnicity and Gender Time 1.

Table A.14.c Medical Record Report of Utilization by Age and Gender Time 2.

Table A.14.d Medical Record Report of Utilization by Ethnicity and Gender Time 2.

Table A.1 Demographic Characteristics of Sleep Study Sample

	Women	Men	All
	% (n)	% (n)	% (n)
Age 20-29	7.7 (27)	1.4 (20)	2.7 (47)
Age 30-39	12.9 (45)	3.8 (53)	5.6 (98)
Age 40-49	30.1 (105)	11.8 (167)	15.5 (272)
Age 50-59	22.4 (78)	20.3 (287)	20.7 (365)
Age 60-69	11.2 (39)	17.9 (252)	16.5 (291)
Age 70-79	5.4 (19)	20.0 (283)	17.2 (302)
Age 80+	10.3 (36)	24.8 (350)	21.9 (386)
Total	100 (349)	100 (1412)	100 (1761)
Hispanic	2.6 (9)	2.3 (32)	2.4 (41)
White	74.3 (252)	91.4 (1270)	88.1 (1522)
African American	17.7 (60)	5.6 (78)	8.0 (138)
Native American	4.7 (16)	2.5 (35)	3.0 (51)
Asian American	1.2 (4)	.2 (3)	.4 (7)
Other	2.1 (7)	.2 (3)	.6 (10)
Total	100 (339)	100 (1389)	100 (1728)
BMI < 25	26.3 (89)	17.9 (250)	19.6 (339)
BMI 25-29	29.8 (101)	41.6 (580)	39.3 (681)
BMI > 29	44.0 (149)	40.5 (564)	41.14 (713)
Total	100 (339)	100 (1394)	100 (1733)
Grade School	0 (0)	3.3 (46)	2.6 (46)
Some High School	2.9 (10)	12.9 (180)	10.9 (190)
High School graduate	31.8 (110)	43.2 (604)	40.9 (714)
Some College	43.4 (150)	26.9 (376)	30.2 (526)
College graduate	18.8 (65)	10.3 (144)	12.0 (209)
Graduate School	3.2 (11)	3.4 (48)	3.4 (59)
Total	100 (346)	100 (1398)	100 (1744)
Currently Smokes	31.4 (109)	19.7 (275)	22.0 (384)

Table A.2 Prevalence of definite or probable RLS stratified by age and gender, and corrected for the accuracy of the Johns Hopkins Telephone diagnostic Instrument.

By Gender and Age							Corrected for test accuracy			
Gender/ age	Sample size	# of cases	Prevalence	SE	Lower CL	Upper CL	Preva-lence	SE	Lower CL	Upper CL
F 20	26	10	0.38	0.10	0.20	0.57	0.52	0.10	0.33	0.71
F 30	44	25	0.57	0.07	0.42	0.71	0.88	0.05	0.78	0.98
F 40	105	53	0.50	0.05	0.41	0.60	0.75	0.04	0.67	0.84
F 50	75	40	0.53	0.06	0.42	0.65	0.81	0.05	0.72	0.90
F 60	37	15	0.41	0.08	0.25	0.56	0.56	0.08	0.40	0.72
F 70	18	5	0.28	0.11	0.07	0.48	0.31	0.11	0.10	0.52
F 80	34	9	0.26	0.08	0.12	0.41	0.28	0.08	0.13	0.44
M 20	20	6	0.30	0.10	0.10	0.50	0.35	0.11	0.14	0.56
M 30	53	20	0.38	0.07	0.25	0.51	0.50	0.07	0.37	0.64
M 40	167	75	0.45	0.04	0.37	0.52	0.65	0.04	0.57	0.72
M 50	281	137	0.49	0.03	0.43	0.55	0.72	0.03	0.67	0.77
M 60	246	83	0.34	0.03	0.28	0.40	0.43	0.03	0.36	0.49
M 70	278	77	0.28	0.03	0.22	0.33	0.31	0.03	0.25	0.36
M 80	337	79	0.23	0.02	0.19	0.28	0.22	0.02	0.18	0.27
By Age										
MF 20	46	16	0.35	0.07	0.21	0.49	0.45	0.07	0.30	0.59
MF 30	97	45	0.46	0.05	0.36	0.56	0.67	0.05	0.58	0.77
MF 40	272	128	0.47	0.03	0.41	0.53	0.69	0.03	0.63	0.74
MF 50	356	177	0.50	0.03	0.45	0.55	0.74	0.02	0.69	0.79
MF 60	283	98	0.35	0.03	0.29	0.40	0.44	0.03	0.39	0.50
MF 70	296	82	0.28	0.03	0.23	0.33	0.31	0.03	0.26	0.36
MF 80	371	88	0.24	0.02	0.19	0.28	0.23	0.02	0.19	0.27
By Gender										
F	339	157	0.46	0.03	0.41	0.52	0.67	0.03	0.62	0.72
M	1382	477	0.35	0.01	0.32	0.37	0.44	0.01	0.42	0.47
Total Sample	1721	634	0.37	0.01	0.35	0.39	0.49	0.01	0.46	0.51

Table A.3 Prevalence of definite RLS stratified by age and gender, and corrected for the accuracy of the Johns Hopkins Telephone Diagnostic Instrument.

							Corrected for test accuracy			
Gender/ age	Sample size	# of cases	Prevalence	SE	Lower CL	Upper CL	Preva-lence	SE	Lower CL	Upper CL
F 20	26	5	0.19	0.08	0.04	0.34	0.08	0.05	-0.02	0.19
F 30	44	17	0.39	0.07	0.24	0.53	0.80	0.06	0.68	0.92
F 40	105	38	0.36	0.05	0.27	0.45	0.71	0.04	0.62	0.80
F 50	75	27	0.36	0.06	0.25	0.47	0.70	0.05	0.60	0.81
F 60	37	11	0.30	0.08	0.15	0.44	0.47	0.08	0.31	0.63
F 70	18	3	0.17	0.09	-0.01	0.34	0.00	0.00	0.00	0.00
F 80	34	6	0.18	0.07	0.05	0.30	0.02	0.03	-0.03	0.08
M 20	20	4	0.20	0.09	0.02	0.38	0.11	0.07	-0.03	0.25
M 30	53	12	0.23	0.06	0.11	0.34	0.21	0.06	0.10	0.32
M 40	167	40	0.24	0.03	0.17	0.30	0.26	0.03	0.19	0.32
M 50	281	78	0.28	0.03	0.23	0.33	0.40	0.03	0.34	0.46
M 60	246	52	0.21	0.03	0.16	0.26	0.15	0.02	0.11	0.20
M 70	278	42	0.15	0.02	0.11	0.19	0.00	0.00	0.00	0.00
M 80	337	42	0.12	0.02	0.09	0.16	0.00	0.00	0.00	0.00
By Age										
MF 20	46	9	0.20	0.06	0.08	0.31	0.10	0.04	0.01	0.18
MF 30	97	29	0.30	0.05	0.21	0.39	0.48	0.05	0.38	0.58
MF 40	272	78	0.29	0.03	0.23	0.34	0.43	0.03	0.37	0.49
MF 50	356	105	0.29	0.02	0.25	0.34	0.46	0.03	0.41	0.51
MF 60	283	63	0.22	0.02	0.17	0.27	0.19	0.02	0.15	0.24
MF 70	296	45	0.15	0.02	0.11	0.19	0.00	0.00	0.00	0.00
MF 80	371	48	0.13	0.02	0.10	0.16	0.00	0.00	0.00	0.00
By Gender										
F	339	107	0.32	0.03	0.27	0.37	0.54	0.03	0.49	0.59
M	1382	270	0.20	0.01	0.17	0.22	0.09	0.01	0.08	0.11
							0.00			
Total Sample	1721	377	0.22	0.01	0.20	0.24	0.18	0.01	0.16	0.20

Table A.4 Prevalence of Insomnia and day time sleepiness by age and gender.

Gender/ age	Variable	N	# of cases	Prevalence	SE	Lower CL	Upper CL
F 20	Ins mod	27	4	0.15	0.07	0.01	0.28
	Ins high	27	0	0.00	0.00	0.00	0.00
	Day slp mod	27	8	0.30	0.09	0.12	0.47
	Day slp high	27	0	0.00	0.00	0.00	0.00
F 30	Ins mod	45	14	0.31	0.07	0.18	0.45
	Ins high	45	4	0.09	0.04	0.01	0.17
	Day Slp mod	45	8	0.18	0.06	0.07	0.29
	Day Slp high	45	2	0.04	0.03	-0.02	0.10
F 40	Ins mod	105	30	0.29	0.04	0.20	0.37
	Ins high	105	7	0.07	0.02	0.02	0.11
	Day Slp mod	105	25	0.24	0.04	0.16	0.32
	Day Slp high	105	11	0.10	0.03	0.05	0.16
F 50	Ins mod	78	17	0.22	0.05	0.13	0.31
	Ins high	78	7	0.09	0.03	0.03	0.15
	Day Slp mod	78	14	0.18	0.04	0.09	0.26
	Day Slp high	78	9	0.12	0.04	0.04	0.19
F 60	Ins mod	39	4	0.10	0.05	0.01	0.20
	Ins high	39	1	0.03	0.03	-0.02	0.08
	Day Slp mod	39	9	0.23	0.07	0.10	0.36
	Day Slp high	39	0	0.00	0.00	0.00	0.00
F 70	Ins mod	19	2	0.11	0.07	-0.03	0.24
	Ins high	19	0	0.00	0.00	0.00	0.00
	Day Slp mod	19	3	0.16	0.08	-0.01	0.32
	Day Slp high	19	0	0.00	0.00	0.00	0.00
F 80	Ins mod	36	4	0.11	0.05	0.01	0.21
	Ins high	36	0	0.00	0.00	0.00	0.00
	Day Slp mod	36	6	0.17	0.06	0.04	0.29
	Day Slp high	36	1	0.03	0.03	-0.03	0.08
M 20	Ins mod	20	3	0.15	0.08	-0.01	0.31
	Ins high	20	0	0.00	0.00	0.00	0.00
	Day Slp mod	20	5	0.25	0.10	0.06	0.44
	Day Slp high	20	0	0.00	0.00	0.00	0.00
M 30	Ins mod	53	6	0.11	0.04	0.03	0.20
	Ins high	53	3	0.06	0.03	-0.01	0.12
	Day Slp mod	53	11	0.21	0.06	0.10	0.32
	Day Slp high	53	3	0.06	0.03	-0.01	0.12
M 40	Ins mod	167	32	0.19	0.03	0.13	0.25
	Ins high	167	11	0.07	0.02	0.03	0.10
	Day Slp mod	167	34	0.20	0.03	0.14	0.26
	Day Slp high	167	20	0.12	0.03	0.07	0.17
M 50	Ins mod	287	59	0.21	0.02	0.16	0.25
	Ins high	287	18	0.06	0.01	0.03	0.09
	Day Slp mod	287	64	0.22	0.02	0.17	0.27
	Day Slp high	287	33	0.11	0.02	0.08	0.15

	Variable	N	# of cases	Prevalence	SE	Lower CL	Upper CL
M 60	Ins mod	252	23	0.09	0.02	0.06	0.13
	Ins high	252	7	0.03	0.01	0.01	0.05
	Day Slp mod	252	43	0.17	0.02	0.12	0.22
	Day Slp high	252	21	0.08	0.02	0.05	0.12
M 70	Ins mod	283	19	0.07	0.01	0.04	0.10
	Ins high	283	2	0.01	0.00	0.00	0.02
	Day Slp mod	283	38	0.13	0.02	0.09	0.17
	Day Slp high	283	16	0.06	0.01	0.03	0.08
M 80	Ins mod	350	12	0.03	0.01	0.02	0.05
	Ins high	350	1	0.00	0.00	0.00	0.01
	Day Slp mod	349	48	0.14	0.02	0.10	0.17
	Day Slp high	349	11	0.03	0.01	0.01	0.05
By Age							
MF 20	Ins mod	47	7	0.15	0.05	0.05	0.25
	Ins high	47	0	0.00	0.00	0.00	0.00
	Day Slp mod	47	13	0.28	0.07	0.15	0.40
	Day Slp high	47	0	0.00	0.00	0.00	0.00
MF 30	Ins mod	98	20	0.20	0.04	0.12	0.28
	Ins high	98	7	0.07	0.03	0.02	0.12
	Day Slp mod	98	19	0.19	0.04	0.12	0.27
	Day Slp high	98	5	0.05	0.02	0.01	0.09
MF 40	Ins mod	272	62	0.23	0.03	0.18	0.28
	Ins high	272	18	0.07	0.02	0.04	0.10
	Day Slp mod	272	59	0.22	0.02	0.17	0.27
	Day Slp high	272	31	0.11	0.02	0.08	0.15
MF 50	Ins mod	365	76	0.21	0.02	0.17	0.25
	Ins high	365	25	0.07	0.01	0.04	0.09
	Day Slp mod	365	78	0.21	0.02	0.17	0.26
	Day Slp high	365	42	0.12	0.02	0.08	0.15
MF 60	Ins mod	291	27	0.09	0.02	0.06	0.13
	Ins high	291	8	0.03	0.01	0.01	0.05
	Day Slp mod	291	52	0.18	0.02	0.13	0.22
	Day Slp high	291	21	0.07	0.02	0.04	0.10
MF 70	Ins mod	302	21	0.07	0.01	0.04	0.10
	Ins high	302	2	0.01	0.00	0.00	0.02
	Day Slp mod	302	41	0.14	0.02	0.10	0.17
	Day Slp high	302	16	0.05	0.01	0.03	0.08
MF 80	Ins mod	385	16	0.04	0.01	0.02	0.06
	Ins high	385	1	0.00	0.00	0.00	0.01
	Day Slp mod	385	54	0.14	0.02	0.11	0.17
	Day Slp high	385	12	0.03	0.01	0.01	0.05

By Gender

Variable	N	# of cases	Prevalence	SE	Lower CL	Upper CL	
F	Ins mod	348	75	0.21	0.02	111.63	0.26
	Ins high	348	19	0.05	0.01	0.03	0.08
	Day Slp mod	348	73	0.21	0.02	0.17	0.25
	Day Slp high	348	23	0.07	0.01	0.04	0.09
M	Ins mod	1412	154	0.11	0.01	0.09	0.13
	Ins high	1412	42	0.03	0.00	0.02	0.04
	Day Slp mod	1412	243	0.17	0.01	0.15	0.19
	Day Slp high	1412	104	0.07	0.01	0.06	0.09
Total Sample							
	Ins mod	1761	229	0.13	0.01	0.11	0.15
	Ins high	1761	61	0.03	0.00	0.03	0.04
	Day Slp mod	1761	316	0.18	0.01	0.16	0.20
	Day Slp high	1761	127	0.07	0.01	0.06	0.08

Table A.5. Portion of Sleep Study members meeting CIDI criteria for the DSM-IV diagnosis of mental health and substance disorders, stratified by gender and age.

	Women	Men	All
Major Depression			
Age 20-29	.44 (CI: .26, .63), 12/27	.32 (CI: .11, .52), 6/19	.39 (CI: .25, .53), 18/46
Age 30-39	.41 (CI: .26, .55), 18/44	.23 (CI: .11, .34), 12/53	.31 (CI: .22, .40), 30/97
Age 40-49	.42 (CI: .33, .52), 44/104	.40 (CI: .33, .47), 66/165	.41 (CI: .35, .47), 110/269
Age 50-59	.38 (CI: .28, .49), 30/78	.31 (CI: .26, .37), 90/286	.33 (CI: .28, .38), 120/364
Age 60-69	.15 (CI: .04, .27), 6/39	.12 (CI: .08, .16), 31/250	.13 (CI: .09, .17), 37/289
Age 70-79	.00, 0/19	.06 (CI: .03, .08), 16/282	.05 (CI: .03, .08), 16/301
Age 80+	.11 (CI: .01, .21), 4/36	.05 (CI: .03, .07), 17/347	.05 (CI: .03, .08), 21/383
For all ages	.33 (CI: .28, .38), 114/347*	.17 (CI: .15, .19), 238/1402*	.20 (CI: .18, .22), 352/1749*
Generalized anxiety disorder			
Age 20-29	.22 (CI: .07, .38), 6/27	.00, 0/19	.13 (CI: .03, .23), 6/46
Age 30-39	.26 (CI: .13, .39), 11/42	.17 (CI: .07, .28), 9/52	.21 (CI: .13, .30), 20/94
Age 40-49	.28 (CI: .19, .37), 28/99	.23 (CI: .16, .29), 37/164	.25 (CI: .19, .30), 65/263
Age 50-59	.19 (CI: .10, .28), 15/78	.18 (CI: .13, .22), 49/280	.18 (CI: .14, .22,), 64/358
Age 60-69	.08 (CI: .00, .17), 3/37	.08 (CI: .05, .12), 20/245	.08 (CI: .05, .11), 23/282
Age 70-79	.05 (CI: .00, .15), 1/19	.04 (CI: .02, .06), 11/279	.04 (CI: .02, .06), 12/298
Age 80+	.03 (CI: .00, .08), 1/36	.03 (CI: .01, .05), 10/341	.03 (CI: .01, .05), 11/377
For all ages	.19 (CI: .15, .23), 65/338	.10 (CI: .08, .11), 136/1380	.12 (CI: .10, .13), 201/1718
Specific phobia			
Age 20-29	.11 (CI: .00, .23), 3/27	.37 (CI: .15, .59), 7/19	.22 (CI: .10, .34), 10/46
Age 30-39	.20 (CI: .09, .32), 9/44	.19 (CI: .09, .30), 10/52	.20 (CI: .12, .28), 19/96
Age 40-49	.33 (CI: .24, .42), 34/104	.25 (CI: .18, .32), 41/164	.28 (CI: .23, .33), 75/268
Age 50-59	.28 (CI: .18, .38), 22/78	.19 (CI: .15, .24), 55/285	.21 (CI: .17, .25), 77/363
Age 60-69	.21 (CI: .08, .34), 8/38	.11 (CI: .07, .15), 27/250	.12 (CI: .08, .16), 35/288
Age 70-79	.00, 0/19	.06 (CI: .03, .08), 16/282	.05 (CI: .03, .08), 16/301
Age 80+	.08 (CI: .00, .17), 3/36	.04 (CI: .02, .06), 14/346	.04 (CI: .02, .07), 17/382
For all ages	.23 (CI: .18, .27), 79/346	.12 (CI: .10, .14), 170/1398	.14 (CI: .13, .16), 249/1744
Social phobia			
Age 20-29	.07 (CI: .00, .17), 2/27	.00, 0/19	.04 (CI: .00, .10), 2/46
Age 30-39	.09 (CI: .01, .18), 4/44	.06 (CI: .00, .12), 3/51	.07 (CI: .02, .13), 7/95
Age 40-49	.20 (CI: .12, .28), 21/104	.12 (CI: .07, .17), 19/163	.15 (CI: .11, .19), 40/267
Age 50-59	.13 (CI: .05, .20), 10/78	.09 (CI: .06, .12), 25/284	.10 (CI: .07, .13), 35/362
Age 60-69	.05 (CI: .00, .12), 2/38	.04 (CI: .02, .06), 10/250	.04 (CI: .02, .06), 12/288
Age 70-79	.05 (CI: .00, .15), 1/19	.02 (CI: .00, .03), 5/280	.02 (CI: .00, .04), 6/299
Age 80+	.05 (CI: .00, .08), 1/36	.02 (CI: .01, .04), 7/345	.02 (CI: .01, .04), 8/381
For all ages	.12 (CI: .08, .15), 41/346	.05 (CI: .04, .06), 69/1392	.06 (CI: .05, .07), 110/1738
Agoraphobia			
Age 20-29	.15 (CI: .01, .28), 4/27	.00, 0/19	.09 (CI: .01, .17), 4/46
Age 30-39	.02 (CI: .00, .07), 1/44	.02 (CI: .00, .06), 1/52	.02 (CI: .00, .05), 2/96
Age 40-49	.15 (CI: .08, .22), 16/104	.09 (CI: .05, .14), 15/163	.12 (CI: .08, .15), 31/267
Age 50-59	.05 (CI: .00, .10), 4/78	.08 (CI: .05, .11), 22/284	.07 (CI: .05, .10), 26/362

	Women	Men	All
Age 60-69	.05 (CI: .00, .12), 2/38	.02 (CI: .00, .03), 4/249	.02 (CI: .00, .04), 6/287
Age 70-79	.00, 0/19	.00, 0/281	.00, 0/300
Age 80+	.03 (CI: .00, .08), 1/35	.01 (CI: .00, .03), 5/345	.02 (CI: .00, .03), 6/380
For all ages	.08 (CI: .05, .11), 28/345	.03 (CI: .02, .04), 47/1393	.04 (CI: .03, .05), 75/1738
Panic Attack			
Age 20-29	.19 (CI: .04, .34), 5/26	.03 (CI: .00, .32), 3/19	.18 (CI: .07, .29), 8/45
Age 30-39	.20 (CI: .09, .32), 9/44	.14 (CI: .04 .23), 7/51	.17 (CI: .09, .24), 16/95
Age 40-49	.18 (CI: .11, .26), 19/103	.13 (CI: .08, .18), 21/162	.15 (CI: .11, .19), 40/265
Age 50-59	.11 (CI: .04, .17), 8/76	.09 (CI: .06, .12), 25/284	.09 (CI: .06, .12), 33/360
Age 60-69	.05 (CI: .00, .12), 2/39	.02 (CI: .00, .04), 5/250	.02 (CI: .01, .04), 7/289
Age 70-79	.00, 0/19	.01 (CI: .00, .02), 3/281	.01 (CI: .00, .02), 3/300
Age 80+	.00, 0/36	.00, 0/344	.00, 0/380
For all ages	.12 (CI: .09, .16), 43/343	.05 (CI: .03, .06), 64/1391	.06 (CI: .05, .07), 107/1734
Alcohol Dependence			
Age 20-29	.04 (CI: .00, .11), 1/27	.05 (CI: .00, .15), 1/19	.04 (CI: .00, .10), 2/46
Age 30-39	.09 (CI: .01, .18), 4/44	.08 (CI: .00, .15), 4/52	.08 (CI: .03, .14), 8/96
Age 40-49	.06 (CI: .01, .10), 6/104	.09 (CI: .05, .14), 15/163	.08 (CI: .05, .11), 21/267
Age 50-59	.00, 0/78	.07 (CI: .04, .10), 19/285	.05 (CI: .03, .08), 19/363
Age 60-69	.00, 0/39	.02 (CI: .00, .03), 4/248	.01 (CI: .00, .03), 4/287
Age 70-79	.00, 0/19	.004 (CI: .00, .01), 1/282	.003 (CI: .00, .01), 1/301
Age 80+	.00, 0/36	.00, 0/347	.00, 0/383
For all ages	.03 (CI: .01, .05), 11/349	.03 (CI: .02, .04), 44/1396	.03 (CI: .02, .04), 55/1743
Drug Dependence			
Age 20-29	.00, 0/27	.05 (CI: .00, .15), 1/19	.02, (CI: .00, .06), 1/46
Age 30-39	.02 (CI: .00, .07), 1/44	.02 (CI: .00, .06), 1/52	.02 (CI: .00, .05), 2/96
Age 40-49	.05 (CI: .01, .09), 5/103	.04 (CI: .01, .07), 7/164	.04 (CI: .02, .07), 12/267
Age 50-59	.03 (CI: .00, .06), 2/78	.01 (CI: .00, .03), 4/280	.02 (CI: .00, .03), 6/358
Age 60-69	.00, 0/39	.00, 0/248	.00, 0/287
Age 70-79	.00, 0/19	.00, 0/281	.00, 0/300
Age 80+	.00, 0/36	.003 (CI: .00, .01), 1/342	.003 (CI: .00, .01), 1/378
For all ages	.02 (CI: .01, .04), 8/346	.01 (CI: .00, .02), 14/1386	.01 (CI: .01, .02), 22/1732

* The total number of respondents differs because some respondent chose not to respond to some sets of diagnostic questions.

Table A.6 Conditions capable of causing RLS symptoms (secondary RLS) from medical record and patient report.

	RLS definite		RLS probable and definite	
	Number	%	Number	%
Any anemia	40	11	85	13
Any kidney disease	11	3	22	35
Any movement disorder	1	00.3	2	00.3
Any neuropathy	73	19	161	25
SSRI use	78	21	156	25
Total RLS	377		634	

Table A.7. Diagnosis of RLS at the VA (either on the current problems list or diagnosed in the past but no longer on problems list)

	Definite RLS cases	Probable RLS cases
Diagnosis by VAMC		
No	331 (96%)	685 (97%)
Yes	15 (4%)	22 (3%)
Total	377 (100%)	634 (100%)

Table A.8. Persons ever diagnosed with a sleep problem at the VA stratified by Insomnia Severity Scale scores

	Sleep Study Diagnosis	
Diagnosis of sleep problem by VAMC	Moderate Insomnia	Severe Insomnia
No	160 (70%)	45 (74%)
Yes	69 (30%)	16 (26%)
Total	229	61

Table A.9. Persons ever diagnosed with a sleep problem at the VA stratified by Epworth Sleepiness Scale scores

	Sleep Study Diagnosis	
Diagnosis of sleep problem by VAMC	Severe Daytime Sleepiness	Moderate Daytime Sleepiness
No	81 (64%)	245 (78%)
Yes	46 (36%)	71 (22%)
Total	127	316

Table A.10 Frequency distribution of ambulatory diagnostic groups (ADG's) by gender and age.

	Males - Age Group						
	< = 29	30-39	40-49	50-59	60-69	70-79	80 +
ADG1 Time limited: minor	5	17	78	133	107	79	124
ADG2 Time limited: minor, primary infections	6	22	77	118	95	78	79
ADG3 Time limited: major	0	2	22	45	34	43	43
ADG4 Time limited: major, primary infections	3	7	35	54	29	30	40
ADG5 Allergies	4	6	30	36	36	33	34
ADG6 Asthma	3	4	21	18	13	12	8
ADG7 Likely to recur: discrete	6	27	102	157	118	115	159
ADG8 Likely to recur: discrete infections	3	12	51	81	54	47	54
ADG9 Likely to recur; progressive	0	1	8	35	30	44	38
ADG10 Chronic medical: stable	7	39	160	273	248	282	345
ADG11 Chronic medical; unstable	1	22	102	210	180	223	288
ADG12 Chronic specialty: stable, orthopedic	1	7	27	36	17	24	26
ADG13 Chronic specialty: stable, ear, nose, throat	0	2	22	40	40	51	79
ADG14 Chronic specialty : stable eye	8	16	101	177	148	177	149
ADG16 Chronic specialty: unstable, orthopedic	0	6	24	31	16	12	18
ADG17 Chronic specialty: unstable, ear, nose, throat	0	0	1	0	1	3	1
ADG18 Chronic specialty: unstable, eye	0	8	52	105	104	94	146
ADG20 Dermatologic	4	11	56	112	131	111	128
ADG21 Injuries/adverse events: minor	6	14	46	52	34	28	43
ADG22 Injuries/ adverse events: major	3	15	42	58	44	37	48
ADG23 Psychosocial: time limited, minor	9	21	89	159	81	65	56
ADG24 Psychosocial: recurrent or persistent, stable	9	22	89	144	74	63	68
ADG25 Psychosocial: recurrent or persistent, unstable	2	14	77	87	47	34	39
ADG26 Signs/symptoms: minor	9	25	111	171	140	156	176
ADG27 Signs/symptoms: uncertain	11	30	131	214	172	182	213
ADG28 Signs/symptoms: major	7	25	96	171	149	155	187
ADG29 Discretionary	3	12	58	109	74	70	106
ADG30 See and reassure	0	4	23	46	48	35	50

ADG32 Malignancy	1	1	12	34	34	74	92
ADG34 Dental	4	5	27	52	20	14	23
	Females - Age Group						
	< = 29	30-39	40-49	50-59	60-69	70-79	80 +
ADG1 Time limited: minor	16	27	75	62	25	12	10
ADG2 Time limited: minor, primary infections	19	32	70	51	17	9	7
ADG3 Time limited: major	0	5	21	14	9	1	3
ADG4 Time limited: major, primary infections	0	3	32	17	4	1	2
ADG5 Allergies	6	10	33	21	6	3	6
ADG6 Asthma	4	4	20	16	6	2	3
ADG7 Likely to recur: discrete	10	23	78	59	20	13	18
ADG8 Likely to recur: discrete infections	13	27	69	41	17	4	14
ADG9 Likely to recur; progressive	0	1	8	5	5	2	3
ADG10 Chronic medical: stable	14	35	95	78	39	19	36
ADG11 Chronic medical; unstable	5	13	57	53	21	10	25
ADG12 Chronic specialty: stable, orthopedic	4	5	21	21	6	3	1
ADG13 Chronic specialty: stable, ear, nose, throat	0	1	11	10	6	4	3
ADG14 Chronic specialty : stable eye	8	20	62	52	20	6	8
ADG16 Chronic specialty: unstable, orthopedic	1	3	13	11	1	1	3
ADG18 Chronic specialty: unstable, eye	3	5	26	26	15	7	11
ADG20 Dermatologic	10	13	51	32	18	10	13
ADG21 Injuries/adverse events: minor	8	12	44	29	6	3	2
ADG22 Injuries/ adverse events: major	3	11	30	30	11	2	4
ADG23 Psychosocial: time limited, minor	8	16	58	41	14	3	4
ADG24 Psychosocial: recurrent or persistent, stable	14	26	65	37	13	9	13
ADG25 Psychosocial: recurrent or persistent, unstable	6	18	54	32	6	3	8
ADG26 Signs/symptoms: minor	13	31	87	62	32	10	26
ADG27 Signs/symptoms: uncertain	21	37	90	71	33	17	27
ADG28 Signs/symptoms: major	17	25	82	63	28	14	17
ADG29 Discretionary	5	11	66	48	16	10	9
ADG30 See and reassure	0	8	21	24	8	3	2
ADG32 Malignancy	1	1	10	17	5	7	6

ADG33 Pregnancy	2	2	1	1	0	0	0
ADG34 Dental	5	7	34	14	5	2	1

Note: In assembling the ADG's, the following sleep and RLS related diagnoses were excluded.
307.4 Specific sleep disorder of non-organic origin.
780.5 Sleep disturbances
333.99 includes Restless Legs Syndrome.

Table A.11 Scores on the Veterans SF36 scale stratified by age and gender.

	Women	Men	All
Physical Functioning (PF)			
Age 20-29	76.7, 25.5 (27)	88.5, 14.9 (20)	81.7, 22.2 (47)
Age 30-39	74.1, 25.9 (44)	72.4, 27.4 (52)	73.2, 26.6 (96)
Age 40-49	58.7, 31.9 (105)	65.4, 30.9 (167)	62.8, 31.4 (272)
Age 50-59	51.7, 30.7 (77)	59.3, 29.5 (286)	57.7, 29.9 (363)
Age 60-69	60.9, 33.2 (39)	65.4, 27.4 (250)	64.8, 28.2 (289)
Age 70-79	56.7, 24.6 (19)	67.9, 25.3 (283)	67.2, 25.3 (302)
Age 80+	52.9, 26.4 (36)	64.8, 23.8 (349)	63.7, 24.2 (385)
For all ages	60.0, 30.6 (347)	65.1, 27.2 (1407)	64.1, 27.9 (1754)
Role Physical (RP)			
Age 20-29	77.1, 27.2 (27)	83.4, 23.7 (20)	79.8, 25.7 (47)
Age 30-39	69.3, 29.1 (44)	72.2, 34.7 (53)	70.9, 32.2 (97)
Age 40-49	60.8, 33.5 (105)	65.8, 33.2 (167)	63.9, 33.3 (272)
Age 50-59	60.0, 33.4 (77)	62.1, 34.1 (285)	61.6, 33.9 (362)
Age 60-69	71.2, 32.8 (39)	69.1, 31.5 (251)	69.4, 31.6 (290)
Age 70-79	70.4, 27.5 (19)	75.0, 28.0 (281)	74.7, 28.0 (300)
Age 80+	70.5, 26.2 (36)	73.5, 27.8 (349)	73.3, 27.6 (385)
For all ages	65.6, 31.7 (347)	69.9, 31.1 (1406)	69.1, 31.3 (1753)
Bodily Pain (BP)			
Age 20-29	63.0, 25.1 (27)	62.9, 31.8 (20)	63.0, 27.8 (47)
Age 30-39	51.9,24.5 (44)	57.9, 27.3 (53)	55.2, 26.1 (97)
Age 40-49	43.7, 30.3 (105)	50.7, 27.2 (167)	48.0, 28.6 (272)
Age 50-59	47.0, 23.8 (78)	52.4, 27.2 (286)	51.2, 26.6 (364)
Age 60-69	53.5, 26.3 (39)	60.0, 27.8 (249)	59.1, 27.7 (288)
Age 70-79	57.9, 23.0 (19)	67.5, 25.8 (283)	66.9, 25.7 (302)
Age 80+	61.5, 21.4 (36)	69.2, 24.5 (349)	68.4, 24.3 (385)
For all ages	50.7, 26.8 (348)	61.1, 27.4 (1407)	59.0, 27.6 (1755)
General Health (GH)			
Age 20-29	65.5, 25.5 (27)	65.9, 19.9 (20)	65.7, 23.0 (47)
Age 30-39	59.2, 20.3 (44)	58.0, 24.0 (52)	58.6, 22.3 (96)
Age 40-49	51.3, 26.3 (104)	52.0, 24.3 (165)	51.7, 25.0 (269)
Age 50-59	50.0, 24.4 (78)	51.0, 24.4 (286)	50.8, 24.4 (364)
Age 60-69	59.2, 18.7 (39)	56.3, 21.8 (249)	56.7, 21.4 (288)
Age 70-79	64.4, 19.7 (19)	61.9, 19.7 (281)	62.1, 19.7 (300)
Age 80+	67.6, 16.3 (36)	63.4, 18.5 (345)	63.8, 18.4 (381)
For all ages	56.4, 23.8 (347)	57.8, 22.1 (1398)	57.5, 22.5 (1745)
Vitality (VT)			
Age 20-29	50.7, 24.0 (27)	56.5, 22.5 (20)	53.2, 23.3 (47)
Age 30-39	40.3, 21.1 (44)	55.3, 22.7 (53)	48.5, 23.1 (97)
Age 40-49	37.8, 25.4 (105)	44.5, 25.1 (166)	41.9, 25.4 (271)
Age 50-59	36.7, 22.3 (78)	44.5, 23.7 (286)	42.8, 23.6 (364)
Age 60-69	53.5, 24.4 (39)	52.9, 25.3 (249)	53.0, 25.2 (288)
Age 70-79	50.5, 22.5 (19)	59.6, 22.8 (283)	59.0, 22.8 (302)
Age 80+	50.0, 18.8 (36)	56.5, 21.3 (347)	55.9, 21.2 (383)
For all ages	42.6, 23.9 (348)	52.6, 24.1 (1404)	50.6, 24.4 (1752)
Social Functioning (SF)			

	Women	Men	All
Age 20-29	64.4, 33.0 (27)	80.6, 24.2 (20)	71.3, 30.4 (47)
Age 30-39	65.9, 27.0 (44)	74.1, 30.6 (53)	70.4, 29.2 (97)
Age 40-49	57.2, 32.7 (104)	68.0, 30.7 (167)	63.8, 31.9 (271)
Age 50-59	69.1, 27.1 (78)	69.6, 29.0 (286)	69.5, 28.6 (364)
Age 60-69	78.5, 30.7 (39)	78.7, 24.2 (250)	78.7, 25.1 (289)
Age 70-79	88.8, 21.6 (19)	84.3, 22.2 (282)	84.6, 22.1 (301)
Age 80+	82.3, 18.3 (36)	84.7, 20.7 (347)	84.5, 20.5 (383)
For all ages	68.3, 30.2 (347)	78.0, 26.1 (1405)	76.1, 27.2 (1752)
Role Emotional (RE)			
Age 20-29	67.9, 34.4 (27)	85.0, 21.6 (20)	75.2, 30.6 (47)
Age 30-39	75.3, 27.4 (44)	87.9, 23.0 (53)	82.2, 25.8 (97)
Age 40-49	69.3, 35.5 (104)	74.8, 31.8 (167)	72.7, 33.3 (271)
Age 50-59	70.5, 32.0 (78)	78.6, 28.8 (265)	76.9, 29.7 (363)
Age 60-69	82.7, 26.9 (39)	86.1, 23.8 (250)	85.6, 24.2 (289)
Age 70-79	91.2, 17.9 (19)	91.3, 19.1 (282)	91.3, 19.0 (301)
Age 80+	89.2, 18.6 (36)	92.5, 15.8 (348)	92.2, 16.1 (384)
For all ages	75.0, 31.3 (347)	85.9, 24.3 (1405)	83.7, 26.2 (1752)
Mental Health (MH)			
Age 20-29	64.1, 22.5 (27)	71.6, 20.9 (20)	67.3, 21.9 (47)
Age 30-39	64.4, 21.7 (44)	73.1, 22.5 (53)	69.1, 22.4 (97)
Age 40-49	59.2, 26.8 (105)	66.1, 23.2 (166)	63.4, 24.8 (271)
Age 50-59	65.4, 21.8 (78)	66.5, 22.9 (286)	66.3, 22.6 (364)
Age 60-69	73.6, 20.2 (39)	75.4, 19.9 (249)	75.1, 19.9 (288)
Age 70-79	78.9, 14.6 (19)	80.9, 15.6 (283)	80.8, 15.5 (302)
Age 80+	77.4, 15.5 (36)	81.1, 15.1 (347)	80.8, 15.2 (383)
For all ages	66.2, 23.3 (348)	74.9, 20.3 (1404)	73.1, 21.2 (1752)
Physical Health Composite Score (PCS)			
Age 20-29	47.6, 10.1 (27)	48.6, 8.7 (20)	48.0, 9.5 47
Age 30-39	43.4, 10.7 (44)	42.4, 12.8 (52)	42.9, 11.8 (96)
Age 40-49	38.7, 12.4 (102)	40.2, 11.8 (165)	39.6, 12.0 (267)
Age 50-59	36.7, 12.0 (76)	38.6, 11.8 (285)	38.2, 11.8 (361)
Age 60-69	40.0, 12.0 (39)	40.8, 11.7 (247)	40.7, 11.7 (286)
Age 70-79	39.1, 8.5 (19)	42.7, 10.0 (278)	42.5, 9.9 (297)
Age 80+	39.7,8.7 (36)	42.2, 9.5 (342)	41.9, 9.5 (378)
For all ages	39.8, 11.6 (343)	41.2, 11.0 (1389)	40.9, 11.2 (1732)
Mental Health Composite Score (MCS)			
Age 20-29	43.4, 13.9 (27)	48.8, 10.8 (20)	45.7, 12.8 (47)
Age 30-39	44.5, 11.7 (44)	50.8, 11.9 (52)	47.9, 12.1 (96)
Age 40-49	43.3, 13.9 (102)	46.6, 11.8 (165)	45.4, 12.7 (267)
Age 50-59	47.1, 11.0 (76)	48.2, 11.4 (285)	48.0, 11.3 (361)
Age 60-69	52.1, 10.2 (39)	52.4, 9.6 (247)	52.3, 9.7 (286)
Age 70-79	55.8, 7.4 (19)	55.3, 7.9 (278)	55.3, 7.9 (297)
Age 80+	54.5, 6.8 (36)	55.4, 6.7 (342)	55.3, 6.7 (378)
For all ages	47.2, 12.4 (343)	52.1, 10.1 (1389)	51.1, 10.8 (1732)

Table A.12.a Spearman Correlations between probability of DSM-IV diagnosis assigned by CIDI score and SF36 mental health scales.

		Mental Health Composite Score (MCS)	Mental Health subscale	Role Emotional subscale	Vitality subscale	Social Functioning subscale
CIDI scale		MCS	MH	RE	VT	SF
Major Depression (prob. of case)	Rho P N	-0.52 <.0001 1723	-0.50 <.0001 1739	-0.48 <.0001 1737	-0.41 <.0001 1739	-0.47 <.0001 1738
General Anxiety Disorder (case)	Rho P N	-0.45 <.0001 1701	-0.46 <.0001 1716	-0.47 <.0001 1714	-0.33 <.0001 1716	-0.39 <.0001 1713
Specific Phobia (prob. of case)	Rho P N	-0.25 <.0001 1725	-0.25 <.0001 1741	-0.21 <.0001 1739	-0.23 <.0001 1741	-0.20 <.0001 1739
Social Phobia (prob. of case)	Rho P N	-0.26 <.0001 1719	-0.26 <.0001 1735	-0.27 <.0001 1733	-0.20 <.0001 1735	-0.23 <.0001 1733
Agoraphobia (prob. of case)	Rho P N	-0.23 <.0001 1719	-0.24 <.0001 1735	-0.22 <.0001 1733	-0.20 <.0001 1735	-0.22 <.0001 1733
Panic Disorder (prob. of case)	Rho P N	-0.26 <.0001 1708	-0.24 <.0001 1723	-0.26 <.0001 1722	-0.20 <.0001 1723	-0.24 <.0001 1721
Alcohol Dependence (prob. of case)	Rho P N	-0.17 <.0001 1723	-0.16 <.0001 1739	-0.11 <.0001 1738	-0.07 .0024 1739	-0.13 <.0001 1738
Drug Dependence (prob. of case)	Rho P N	-0.16 <.0001 1712	-0.15 <.0001 1728	-0.16 <.0001 1727	-0.10 <.0001 1728	-0.17 <.0001 1727

Table A.12.b Spearman Correlations between probability of DSM-IV diagnosis assigned by CIDI score and SF36 physical health scales.

		Physical Health score (PCS)	Physical Functioning subscale	Role Physical subscale	Bodily Pain subscale	General Health subscale
CIDI scale		PCS	PF	RP	BP	GH
Major Depression (prob. of case)	Rho P N	-0.22 <.0001 1723	-0.25 <.0001 1739	-0.30 <.0001 1738	-0.36 <.0001 1740	-0.31 <.0001 1736
General Anxiety Disorder (case)	Rho P N	-0.16 <.0001 1701	-0.20 <.0001 1715	-0.26 <.0001 1715	-0.28 <.0001 1717	-0.28 <.0001 1711
Specific Phobia (prob. of case)	Rho P N	-0.11 <.0001 1725	-0.12 <.0001 1741	-0.14 <.0001 1740	-0.18 <.0001 1742	-0.16 <.0001 1737
Social Phobia (prob. of case)	Rho P N	-0.11 <.0001 1719	-0.13 <.0001 1735	-0.15 <.0001 1734	-0.19 <.0001 1736	-0.18 <.0001 1731
Agoraphobia (prob. of case)	Rho P N	-0.13 <.0001 1719	-0.15 <.0001 1735	-0.18 <.0001 1734	-0.17 <.0001 1736	-0.17 <.0001 1731
Panic Disorder (prob. of case)	Rho P N	-0.09 .0003 1708	-0.09 .0002 1723	-0.13 <.0001 1723	-0.18 <.0001 1724	-0.13 <.0001 1719
Alcohol Dependence (prob. of case)	Rho P N	0.02 .36 1723	0.02 .53 1740	-0.02 .36 1739	-0.04 .07 1741	-0.04 .13 1736
Drug Dependence (prob. of case)	Rho P N	-0.04 .07 1712	-0.04 .07 1729	-0.08 .0007 1728	-0.11 <.0001 1730	-0.09 .0002 1725

Table A.13 Percent of insomnia among study members which can be attributed to RLS (population attributable fraction) using unadjusted or adjusted RLS prevalence estimates and two methods of PAR calculation.

Definite RLS	RLS def prevalence unadjusted	RLS def adjusted prevalence (using validation study)	Proportion of Insomnia cases exposed to RLS	Relative Risk* of insomnia given RLS	Levin's Attributable Risk using unadjusted prevalence (%).	Levin's Attributable Risk using adjusted prevalence (%).	Kleinbaum's Population Attributable Fraction (%)
Severe Insomnia	0.22	0.18	0.30	0.99	-0.22	-0.18	-0.30
Moderate or Severe Insomnia	0.22	0.18	0.37	1.48	9.52	8.02	12.09
Moderate Insomnia	0.22	0.18	0.39	1.66	12.63	10.71	15.66

Probable or Definite RLS	RLS prob or def prevalence unadjusted	RLS def/prob adjusted prevalence (using validation study)	Proportion of Insomnia cases exposed to prob/def RLS	Relative Risk* of insomnia give RLS	Levin's Attributable Risk using unadjusted prevalence (%).	Levin's Attributable Risk using adjusted prevalence (%) .	Kleinbaum's Population Attributable Risk (%)
Severe Insomnia	0.37	0.49	0.54	1.07	2.51	3.30	3.54
Moderate or Severe Insomnia	0.37	0.49	0.57	1.48	15.03	18.95	18.65
Moderate Insomnia	0.37	0.49	0.58	1.62	18.59	23.19	22.35

* Relative risk estimates are adjusted for age, gender, ADG groups, and SF36 composite physical score (PCS).

Table A.14.a Medical Record plus Interview Report of Utilization by Age and Gender – Time 1 (continued)

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Prescriptions (all Rx 2 months prior and 1 month after interview)									
Age 20-29	3.7	5.07	27	1.5	1.73	20	2.77	4.12	47
Age 30-39	4.82	4.96	45	4.55	5.17	53	4.67	5.05	98
Age 40-49	9.21	11.71	105	7.57	7.79	167	8.2	9.5	272
Age 50-59	8.67	7.43	78	7.84	6.92	287	8.02	7.03	365
Age 60-69	8.28	6.35	39	7.27	6.77	252	7.41	6.71	291
Age 70-79	6.63	7.48	19	6.56	4.83	283	6.56	5.02	302
Age 80-89	8	5.32	36	6	4.84	350	6.19	4.91	386
All ages	7.02	8.46	348	6.78	6.13	1412	6.98	6.66	1761

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Diagnostic Procedures (Medical Records and Interview - includes radiology)									
Age 20-29	0.15	0.46	27	0.25	0.64	20	0.19	0.54	47
Age 30-39	0.38	0.75	45	0.36	0.81	53	0.37	0.78	98
Age 40-49	0.7	1.39	105	0.46	0.85	167	0.55	1.1	272
Age 50-59	0.6	1.1	78	0.62	1.08	287	0.61	1.08	365
Age 60-69	0.67	0.9	39	0.55	0.88	252	0.56	0.88	291
Age 70-79	0.68	0.75	19	0.68	1	283	0.68	0.99	302
Age 80-89	0.67	0.093	36	0.65	0.99	350	0.65	0.98	386
All ages	0.58	1.08	349	0.59	0.97	1412	0.59	0.99	1761

Table A.14.a Medical Record plus Interview Report of Utilization by Age and Gender – Time 1 (continued)

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Hospitalizations LOS (VA and not -VA)									
Age 20-29	0	0	27	0	0	20	0	0	47
Age 30-39	0.07	0.45	45	0	0	53	0.03	0.3	98
Age 40-49	0.17	0.91	105	0.04	0.33	167	0.09	0.63	272
Age 50-59	0.23	1.82	78	0.08	0.64	287	0.12	1.01	365
Age 60-69	0	0	39	0.23	1.48	252	0.2	1.38	291
Age 70-79	0	0	19	0.35	3.52	283	0.33	3.41	302
Age 80-89	0.14	0.68	36	0.05	0.39	350	0.06	0.43	386
All ages	0.13	1.03	349	0.15	1.74	1412	0.14	1.62	1761

Table A.14.b Medical Record Report of Utilization by Ethnicity and Gender - Time 1

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Primary Care Physician Visits (medical record and interview)									
White	1.31	0.91	267	1.29	0.71	1298	1.3	0.75	1565
African Am	1.31	1.09	65	1.39	0.93	79	1.4	1	144
Native Am	1.5	1.29	4	1.1	0.32	10	1.21	0.7	14
Asian Am	2.33	1.53	3	1	0	2	1.8	1.3	5
Hispanic	1.67	1	9	1.22	0.61	32	1.32	0.72	41

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Visits to Specialist Physicians (medical record and interview)									
White	1.06	2.32	267	0.67	1.29	1298	0.74	1.52	1565
African Am	1.86	3.99	65	0.66	1.53	79	1.2	2.96	144
Native Am	1.25	1.26	4	0.4	0.7	10	0.64	0.92	14
Asian Am	0.33	0.58	3	0.5	0.71	2	0.4	0.55	5
Hispanic	0.33	1	9	1.03	1.4	32	0.88	1.35	41

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Prescriptions (all Rx 2 months prior and 1 month after interview)									
White	8.04	9.03	266	6.85	6.19	1298	7.06	6.77	1564
African Am	7.02	6.31	65	6.27	5.63	79	6.6	5.93	144
Native Am	5.75	5.44	4	6.7	6.02	10	6.43	5.67	14
Asian Am	4.67	3.51	3	8.5	7.78	2	6.2	5.07	5
Hispanic	5.78	9.27	9	7.5	5.46	32	7.12	6.39	41

Table A.14.b Medical Record Report of Utilization by Ethnicity and Gender - Time 1 (continued)

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Diagnostic Procedures (Medical Records and Interview - includes radiology)									
White	0.58	1.06	267	0.61	0.98	1298	0.6	0.99	1565
African Am	0.74	1.23	65	0.49	0.92	79	0.6	1.07	144
Native Am	0	0	4	0.1	0.32	10	0.07	0.27	14
Asian Am	0	0	3	0.5	0.71	2	0.2	0.45	5
Hispanic	0.78	0.83	9	0.5	0.84	32	0.56	0.84	41

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Hospitalizations LOS (VA and not -VA)									
White	0.03	0.27	267	0.14	1.79	1298	0.12	1.64	1565
African Am	0.06	0.5	65	0.11	0.91	79	0.09	0.75	144
Native Am	0	0	4	0	0	10	0	0	14
Asian Am	0	0	3	0	0	2	0	0	5
Hispanic	0	0	9	0	0	32	0	0	41

Table A.14.c Time 2 Medical Record Report of Utilization by Age and Gender

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Primary Care Physician Visits (medical record and interview)									
Age 20-29	0.52	0.75	27	0.1	0.31	20	0.34	0.64	47
Age 30-39	0.58	0.78	45	0.34	0.62	53	0.45	0.71	98
Age 40-49	0.7	1.14	103	0.6	0.85	167	0.64	0.97	270
Age 50-59	0.83	1.26	76	0.65	1.12	283	0.69	1.15	359
Age 60-69	1.33	2.45	39	0.8	1.07	248	0.87	1.35	287
Age 70-79	0.94	0.8	18	0.87	0.88	273	0.88	0.87	291
Age 80-89	0.69	0.95	36	0.8	0.89	331	0.79	0.89	367
All ages	0.78	1.3	344	0.73	0.96	1375	0.74	1.04	1719

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Visits to Specialist Physicians (medical record and interview)									
Age 20-29	0.33	0.68	27	0.55	1.23	20	0.43	0.95	47
Age 30-39	0.87	1.87	45	0.34	0.85	53	0.58	1.43	98
Age 40-49	1.04	1.75	102	0.8	1.44	167	0.89	1.57	269
Age 50-59	1.05	1.62	76	0.82	1.67	283	0.87	1.66	359
Age 60-69	0.72	0.94	39	0.61	1.19	248	0.62	1.16	287
Age 70-79	0.94	1.26	18	0.77	1.35	273	0.78	1.34	291
Age 80-89	0.72	0.88	36	0.68	1.2	331	0.69	1.17	367
All ages	0.89	1.5	343	0.71	1.36	1375	0.75	1.39	1718

Table A.14.c Time 2 Medical Record Report of Utilization by Age and Gender (continued)

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Prescriptions (all Rx 2 months prior and 1 month after interview)									
Age 20-29	3	4.5	27	1.8	4.63	20	2.49	4.54	47
Age 30-39	3.11	4.26	45	3.25	5.37	53	3.18	4.87	98
Age 40-49	7.65	8.14	102	6.87	7.9	167	7.16	7.98	269
Age 50-59	7.42	6.9	76	7.32	7.67	283	7.34	7.51	359
Age 60-69	8.31	5.84	39	6.76	6.66	248	6.97	6.57	287
Age 70-79	6.22	6.1	18	5.8	4.44	273	5.82	4.55	291
Age 80-89	6.19	4.29	36	5.46	4.38	331	5.53	4.37	367
All ages	6.48	6.7	343	6.18	6.22	1375	6.24	6.31	1718

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Diagnostic Procedures (Medical Records and Interview - includes radiology)									
Age 20-29	0.3	0.61	27	0.3	0.92	20	0.3	0.75	47
Age 30-39	0.51	0.99	45	0.11	0.47	53	0.3	0.78	98
Age 40-49	0.29	0.8	103	0.35	1.13	167	0.33	1.02	270
Age 50-59	0.41	1.06	76	0.31	0.98	283	0.33	1	359
Age 60-69	0.46	1.05	39	0.26	0.8	248	0.29	0.84	287
Age 70-79	0.28	0.67	18	0.56	1.07	273	0.54	1.05	291
Age 80-89	0.47	0.7	36	0.51	1.11	331	0.5	1.08	367
All ages	0.38	0.89	344	0.39	1.01	1375	0.39	0.99	1719

Table A.14.c Time 2 Medical Record Report of Utilization by Age and Gender (continued)

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Hospitalizations LOS (VA and not VA)									
Age 20-29	0	0	27	0	0	20	0	0	47
Age 30-39	0.04	0.3	45	0	0	53	0.02	0.2	98
Age 40-49	0	0	103	0.21	2.2	167	0.13	1.73	270
Age 50-59	0.01	0.11	76	0.06	0.55	283	0.05	0.49	359
Age 60-69	0	0	39	0.17	1.16	248	0.14	1.08	287
Age 70-79	0	0	18	0.24	1.57	273	0.22	1.53	291
Age 80-89	0.22	0.8	36	0.15	1	331	0.16	0.98	367
All ages	0.03	0.29	344	0.15	1.27	1375	0.13	1.15	1719

Table A.14.d. Time 2 Medical Record Report of Utilization by Ethnicity and Gender

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of PC Physician Visits (medical record and interview)									
White	0.84	1.4	264	0.74	0.97	1263	0.75	1.05	1527
African Am	0.59	0.77	64	0.6	0.91	77	0.6	0.84	141
Native Am	1.5	2.38	4	0.9	0.99	10	1.07	1.44	14
Asian Am	0.33	0.58	3	1.5	0.71	2	0.8	0.84	5
Hispanic	0.78	0.83	9	0.87	1.07	30	0.85	1.01	39

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Visits to Specialist Physicians (medical record and interview)									
White	0.84	1.34	263	0.74	1.38	1263	0.75	1.37	1526
African Am	1.14	2.08	64	0.38	0.87	77	0.72	1.58	141
Native Am	1.5	1.91	4	0.6	0.84	10	0.86	1.23	14
Asian Am	0	0	3	1	0	2	0.4	0.55	5
Hispanic	0.22	0.44	9	1	1.51	30	0.82	1.37	39

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Prescriptions (all Rx 2 months prior and 1 month after interview)									
White	7.01	6.74	263	6.26	6.29	1263	6.39	6.37	1526
African Am	4.42	5.79	64	5.38	5.33	77	4.94	5.54	141
Native Am	6.75	4.03	4	6.9	5.13	10	6.86	4.69	14
Asian Am	1	1	3	7	9.9	2	3.4	5.98	5
Hispanic	4.22	6.18	9	6.87	7.02	30	6.26	6.85	39

Table A.14.d. Time 2 Medical Record Report of Utilization by Ethnicity and Gender (continued)

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Number of Diagnostic Procedures (Medical Records and Interview - includes radiology)									
White	0.41	0.91	264	0.42	1.05	1263	0.42	1.02	1527
African Am	0.28	0.7	64	0.08	0.31	77	0.17	0.53	141
Native Am	1.25	2.5	4	0	0	10	0.36	1.34	14
Asian Am	0.33	0.58	3	0	0	2	0.2	0.45	5
Hispanic	0.44	0.73	9	0.57	0.9	30	0.54	0.85	39

	Women			Men			All		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Hospitalizations LOS (VA and not -VA)									
White	0.04	0.32	264	0.16	1.32	1263	0.14	1.21	1527
African Am	0	0	64	0.06	0.57	77	0.04	0.42	141
Native Am	0.25	0.5	4	0	0	10	0.07	0.27	14
Asian Am	0	0	3	0	0	2	0	0	5
Hispanic	0	0	9	0.17	0.65	30	0.13	0.57	39

Appendix B Abstracts presented at scientific meetings.

Abstract presented at the Research and Education Forum of the Ohio Academy of Family Physicians, Columbus, Ohio, April, 2003.

The Prevalence and Outcomes of Restless Legs Syndrome among Patients at VA Primary Care Clinics. Baughman K., Panzner M., Ober S., Bourguet C., Steiner R. Louis Stokes Department of Veterans Affairs Medical Center, Brecksville, OH 44141

Introduction: Restless Legs Syndrome (RLS) is a sensori-motor disorder characterized by unpleasant, abnormal feelings in the legs and occasionally arms which occur at rest or when initiating sleep, and in the evening or at night. RLS interferes with the ability to fall asleep or maintain sleep. The goal of this research is to estimate the prevalence of RLS and insomnia among patients seen at VA primary care clinics. This research investigates an explanatory model in which RLS contributes to insomnia. Insomnia contributes to diminished mental health status and to increased health care utilization. **Methods:** Study members were representative of Veterans seen at primary care clinics affiliated with the Cleveland VA Medical Center. A telephone survey was used to determine the prevalence of RLS and insomnia. Patients were classified as non-RLS cases, probable or definite cases. Health status was measured using the Mental and Physical Composite Scales (MCS and PCS) of the SF12. Utilization information was obtained from the patient and included: number of office visits, diagnostic procedures, hospitalizations, and surgical procedures. All tests of hypothesized relationships were adjusted for age, gender, Body Mass Index, and physical health status (PCS score). **Results:** Preliminary results from 620 patients are reported. Forty-five percent of patients who were approached completed an interview. The sample included 544 men and 76 women, age range 25 to 89 years. Among men, the prevalence of probable RLS was 15.8%, definite RLS was 9.7%, moderate insomnia was 9.9% and severe insomnia was 3.3%. Among women, the prevalence of probable RLS was 19.7%, definite RLS was 14.5%, moderate insomnia was 26.3%, and severe insomnia was 7.9%. The insomnia score of an average patient increased 53% in the presence of definite RLS ($p < .001$). The mean MCS score was 50.3, similar to the US population mean. The mean PCS score was 39.9, one standard deviation below the US mean. The mean MCS score of persons with probable or definite RLS was significantly lower (41.0, $p<.01$), as was the mean MCS score of persons with moderate insomnia (40.6, $p <.0001$) and of persons with severe insomnia (34.7, $p<.0001$). As hypothesized, the association between RLS and the MCS disappeared when insomnia was included in the regression model. Analysis of utilization data obtained from patients found that neither insomnia nor RLS was associated with physicians visits. RLS but not insomnia was positively associated ($p = .04$) with diagnostic testing. **Conclusions:** Preliminary analysis of approximately one third of the planned sample offered support for the hypothesized model in which RLS impacts health outcomes and utilization through insomnia. **Support:** Supported by the US Army Medical Research and Materiel Command under DAMD17-03-1-0082.

Presented at the meeting of the Associated Professional Sleep Societies in Philadelphia, June, 2004.

The Prevalence and Outcomes of Restless Legs Syndrome among Veterans.

Ober SK, Bourguet CC, Baughman KR, Steiner RP, and Shapiro, HD.

Introduction: Restless Legs Syndrome (RLS) is a sensori-motor disorder characterized by unpleasant, abnormal feelings in the legs and occasionally arms which occur at rest or when initiating sleep, and in the evening or at night. Sufferers experience an uncontrollable urge to move to relieve these symptoms. RLS interferes with the ability to fall asleep or maintain sleep. Estimates of the prevalence of RLS in community populations ranges from 4% to 17%. A 29% prevalence has been reported in one VA outpatient sample. The goal of this research is to estimate the prevalence of RLS and insomnia among patients seen at VA primary care clinics. This research investigates an explanatory model in which RLS contributes to insomnia. Insomnia contributes to diminished mental health status and to increased health care utilization. **Methods:** Study members were a representative sample of Veterans seen at Community Based Outpatient Clinics affiliated with the Louis B. Stokes Cleveland VA Medical Center in Ohio. A cross-sectional telephone survey was used to determine the prevalence of RLS and insomnia. Patients were classified as non-RLS cases, probable (3 criteria) or definite (4 criteria) cases. Health status was measured using the Mental and Physical Composite Scales (MCS and PCS) of the SF12. Utilization information was obtained from the patient and included: number of office visits, diagnostic procedures, hospitalizations, and surgical procedures. All tests of hypothesized relationships were adjusted for age, gender, Body Mass Index, and physical health status (PCS score). **Results:** Preliminary results from 620 patients are reported. Forty-five percent of patients who were approached completed an interview. The sample included 544 men and 76 women, age range 25 to 89 years. Among men, the prevalence of probable RLS was 15.8%, definite RLS was 9.7%, moderate insomnia was 9.9% and severe insomnia was 3.3%. Among women, the prevalence of probable RLS was 19.7%, definite RLS was 14.5%, moderate insomnia was 26.3%, and severe insomnia was 7.9%. The insomnia score of an average patient increased 53% in the presence of 4 RLS symptoms ($p < .001$). In this VA sample, the mean MCS score was 50.3, similar to the US population mean. The mean PCS score was 39.9, one standard deviation below the US mean. The mean MCS score of persons with probable or definite RLS was significantly lower (41.0, $p<.01$), as was the mean MCS score of persons with moderate insomnia (40.6, $p <.0001$) and of persons with severe insomnia (34.7, $p<.0001$). As hypothesized, the association between RLS and the MCS disappeared when insomnia was included in the regression model. Analysis of utilization data obtained from patients found that neither insomnia nor RLS were associated with physicians visits. RLS but not insomnia was positively associated ($p = .04$) with diagnostic testing. **Conclusions:** Preliminary analysis of approximately one third of the planned sample offered support for the hypothesized explanatory model. The final sample (n=1914) will allow precise estimates of RLS prevalence in age strata. **Support:** Supported by the US Army Medical Research and Materiel Command under DAMD17-03-1-0082.

Abstract presented at the Peer Reviewed Medical Research Program Military Health Research Forum (Investigators' Meeting), San Juan, Puerto Rico, April, 2004.

THE PREVALENCE AND OUTCOMES OF RESTLESS LEGS SYNDROME AMONG VETERANS. Bourguet CC, Ober SK, Baughman KR, Steiner RP, Shapiro, HD. The Northeastern Ohio Universities College of Medicine.

BACKGROUND/ PURPOSE: Restless Legs Syndrome (RLS) is a sensori-motor disorder characterized by unpleasant, abnormal feelings in the legs and occasionally arms which occur at rest or when initiating sleep, and in the evening or at night. The sufferer experiences an uncontrollable urge to move in order to relieve these symptoms. RLS interferes with the ability to fall asleep or maintain sleep. Estimates of the prevalence of RLS in community populations ranges from 4% to 17%. A 29% prevalence has been reported in one VA outpatient sample. The goal of this research is to estimate the prevalence of RLS and insomnia among patients seen at VA primary care outpatient clinics. This research investigates an explanatory model in which RLS contributes to insomnia. Insomnia contributes to diminished mental health status, and diminished mental health status leads to increased health care utilization. **METHODS:** Study members are a representative sample (final sample size = 1914) of Veterans seen at Community Based Outpatient Clinics affiliated with the Louis B. Stokes Cleveland VA Medical Center in Ohio. A cross-sectional telephone survey is being used to determine the prevalence of RLS and insomnia. Patients are classified as non-RLS cases, probable (3 criteria) or definite (4 criteria) cases. Health measures include the Mental and Physical Composite Scales (MCS and PCS) of the SF12, the WHO's Composite International Diagnostic Index (Short Form), and the problem list from the medical record. Utilization measures will be obtained from the patient and the medical record and include: number of office visits, diagnostic procedures, prescribed medications, hospitalizations, and surgical procedures. Additional utilization data will be collected at one year follow-up. All data analysis includes adjustment for age, gender, Body Mass Index, and physical health status (PCS score). **RESULTS:** Preliminary results from 620 patients are reported here. Forty-five percent of patients who were approached completed an interview. The sample includes 544 men and 76 women, age range 25 to 89 years. Among men, the prevalence of probable RLS is 15.8%, definite RLS is 9.7%, moderate insomnia is 9.9% and severe insomnia is 3.3%. Among women, the prevalence of probable RLS is 19.7%, definite RLS is 14.5%, moderate insomnia is 26.3%, and severe insomnia is 7.9%. The insomnia score of an average patient increases 53% in the presence of 4 RLS symptoms ($p < .001$). In this VA sample, the mean MCS scores is 50.3, similar to the US population mean. The mean PCS score is 39.9, one standard deviation below the US mean. The mean MCS score of persons with probable or definite RLS is significantly lower (41.0, $p<.01$), as is the mean MCS score of persons with moderate insomnia (40.6, $p <.0001$) and of persons with severe insomnia (34.7, $p<.0001$). As hypothesized, the association between RLS and the MCS disappears when insomnia is included in the regression model. Analysis of utilization data obtained from patients finds that neither insomnia nor RLS is associated with physicians visits. RLS but not insomnia is positively associated ($p=.04$) with diagnostic testing. **CONCLUSION:** Preliminary analysis of approximately one third of the planned sample offers support for the hypothesized explanatory model. The final sample will allow precise estimates of RLS prevalence in age strata. Data obtained from medical records will allow improved adjustment for health status and more definitive conclusions about the relationship between sleep disorders and health care utilization.

THE U.S. ARMY MEDICAL RESEARCH MATERIEL COMMAND UNDER DAMD17-03-1-0082 SUPPORTED THIS WORK.

Paper presented at the meeting of the Society for Epidemiologic Research, Toronto, Ontario, Canada, June, 2005

Insomnia and Daytime Sleepiness: Risk Attributable to Restless Legs Syndrome, BMI, Smoking, and Alcohol among VA Outpatients.

*C.C. Bourguet, R.P. Steiner, S.K. Ober, K.R. Baughman, H.D. Shapiro. (N. E. Ohio Universities College of Medicine, Rootstown, OH 44272)

Insomnia and daytime sleepiness are common among patients with Restless Legs Syndrome (RLS). This research was planned to estimate the prevalence of insomnia and daytime sleepiness and to estimate the contribution of RLS and other behavioral factors to these complaints in primary care patients.

Telephone interviews were conducted with 1761 patients recruited at 12 VA primary care clinics in Ohio. Measures of RLS, insomnia, daytime sleepiness, alcohol dependence, smoking and BMI were included. Logistic regression was used to obtain odds ratios that, with risk factor prevalence, estimated attributable risks (AR).

Patients were aged 22 to 92. Eighty percent of the sample were male, 41% had a BMI of 30 or over, and 46% had post high school education. The prevalence of RLS symptoms at least once per week was 21% for women and 13% for men. Moderate or severe insomnia was more common in women (27% compared to 14% for men). Both genders had a 7% prevalence of daytime sleepiness. In predicting insomnia, the attributable risk was 22% ($p<.0001$) for RLS, 27% ($p=.003$) for a BMI of 30 or over, 4% ($p=.007$) for alcohol dependence, and 6% ($p=.12$) for smoking. In predicting daytime sleepiness, the AR for insomnia was 28% ($p<.0001$) and 7% ($p=.006$) for RLS. Obesity, smoking, and alcohol dependence did not have a significant relationship to daytime sleepiness beyond their effects on insomnia. Only 10 of the 243 patients who reported RLS symptoms had received a diagnosis.

RLS, obesity, alcohol dependence, and gender, are significant risk factors for insomnia. Insomnia, in turn, is a significant risk factor for daytime sleepiness. RLS is a significant risk factor for daytime sleepiness, even after controlling for insomnia. Despite the impact of RLS on insomnia and daytime sleepiness, few patients are diagnosed with RLS by their physicians.

Supported by the US Army Medical Research and Materiel Command and Pfizer Pharmaceutical Corporation.

Poster presented at the meeting of the Associated Professional Sleep Societies, Denver, June, 2005.

Title: Insomnia and Daytime Sleepiness: Risk Attributable to RLS, BMI, Smoking, and Alcohol in a VA Outpatient Population

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Introduction: Insomnia and daytime sleepiness are common among patients with Restless Legs Syndrome (RLS). The goal of this research was to estimate the prevalence of insomnia and daytime sleepiness and to estimate the contribution of RLS and other behavioral factors to these complaints in primary care patients.

Methods: Telephone interviews were conducted with 1761 patients recruited at 12 VA primary care clinics in Ohio. Measures of RLS, insomnia, daytime sleepiness, alcohol dependence, smoking and BMI were included. Logistic regression was used to obtain odds ratios that were used with risk factor prevalence to estimate attributable risks (AR).

Results: Patients were aged 22 to 92. Eighty percent of the sample were male, 41% had a BMI of 30 or over, and 46% had post high school education. The prevalence of RLS symptoms at least once per week was 21% for women and 13% for men. Moderate or severe insomnia was more common in women (27% compared to 14% for men). Both genders had a 7% prevalence of daytime sleepiness. In predicting insomnia, the attributable risk was 22% ($p<.0001$) for RLS, 27% ($p=.003$) for a BMI of 30 or over, 4% ($p=.007$) for alcohol dependence, and 6% ($p=.12$) for smoking. In predicting daytime sleepiness, the AR for insomnia was 27% ($p<.0001$) and 7% ($p=.006$) for RLS. Obesity, smoking, and alcohol dependence did not have a significant relationship to daytime sleepiness beyond their effects on insomnia. Only 10 of the 243 patients who reported RLS symptoms had been diagnosed with RLS.

Conclusion: RLS, obesity, alcohol dependence, and gender, are significant risk factors for insomnia. Insomnia, in turn, is a significant risk factor for daytime sleepiness. RLS is a significant risk factor for daytime sleepiness, even after controlling for insomnia. Despite the impact of RLS on insomnia and daytime sleepiness, few patients are diagnosed with RLS by their physicians.

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Abstracts (two) presented at the meeting of the Associated Professional Sleep Societies, June, 2007 in Minneapolis, MN.

Accuracy and Reproducibility of the Johns Hopkins Telephone Diagnostic Instrument for Restless Legs Syndrome.

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Introduction. A need exists for a valid and reliable instrument to identify RLS cases in epidemiologic studies. This instrument would employ the criteria of the IRLSSG and, when administered by trained non-physician interviewers, would accurately identify RLS cases who have not been previously diagnosed. We evaluated the Johns Hopkins Telephone Diagnostic Instrument (TDI) using these criteria.

Methods. Study members were veterans who were recruited at an office visit to a VA outpatient clinic. They were participants in a larger study of RLS and had previously completed the TDI by telephone with a trained non-clinician (Time 1). The TDI was re-administered face to face by a nurse (Time 2). The gold standard was a diagnostic interview conducted by a physician. We calculated the reproducibility of the TDI between two administrations, and the sensitivity and specificity of the TDI at two time points relative to the gold standard.

Results. Eighty-five (39%) of eligible patients completed both TDI's and 74 (34%) completed the entire study. They were predominantly male (88%) and Caucasian (89%). The mean interval from Time 1 to Time 2 TDI was 13.9 months (range: 3-25 months). Reproducibility was low (kappa = 0.34, $p<.01$), but was higher for interviews repeated within one year (kappa = 0.55, $p< .01$). By gold standard, 43% were definite cases and 11% were probable cases. Including those reporting => 3 symptoms as cases, sensitivity of the TDI ranged from 63% (Time 1) to 75% (Time 2). Specificity ranged from 88% (Time 1) to 71% (Time 2).

Conclusion. The sensitivity and specificity of the TDI have been reported to be over 90%. Previous studies have distinguished diagnosed cases from non-cases. The lower accuracy which we report likely results from greater symptom overlap between previously undiagnosed cases and normals. These results are applicable to epidemiologic studies in primary care or community settings.

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Title: The Association of Antidepressant Use with Restless Legs Syndrome in a VA Outpatient Population

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Introduction: There has been mixed evidence for an association between antidepressant use and Restless Legs Syndrome (RLS). While people with RLS often experience greater levels of insomnia and depression, it is unclear whether antidepressants exacerbate the symptoms of RLS. Our goal was to clarify the relationship.

Methods: Telephone interviews were conducted with 1761 patients recruited at 12 VA primary care clinics in Ohio. Measures of RLS, insomnia, depression, smoking status, and BMI were included. In addition, we obtained medical record data that included drug prescriptions six months prior to the interviews.

Results: Patients were aged 22 to 92. Eighty percent of the sample were male, 41% had a BMI of 30 or over, and 22% currently smoked. The prevalence of RLS symptoms at least once per week was 28% for women and 18% for men. Patients currently using an antidepressant were more likely to have RLS (25%) than were patients not using an antidepressant (19%), ($x^2 = 3.84$, $p = .05$). In particular, those using a tricyclic antidepressant were most likely to have RLS (35%). While SSRIs as a class were not associated with RLS, those using citalopram were more likely to have RLS (35%) than those not using citalopram (20%), ($x^2 = 5.50$, $p = .02$).

Controlling for race, age, gender, BMI, and smoking status, we used logistic regression to predict RLS. In this multivariate analysis tricyclics and SSRIs were not significantly associated with RLS. However, when we examined individual drugs, citalopram had a significant association with RLS ($p = .02$, OR=1.023). This relationship disappeared when we controlled for depression and insomnia.

Conclusion: The relationship between antidepressant use and RLS is likely to be a result of RLS patients experiencing greater levels of insomnia and depression. In multivariate analyses that control for insomnia and depression, the association between RLS and antidepressant use fades.

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Appendix C. Manuscript based on Task 4.

Submitted to the Journal, Sleep Medicine, in August, 2007.

Reproducibility and Accuracy of the Johns Hopkins Telephone Diagnostic Interview for Restless Legs Syndrome.

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Keywords: Restless Legs Syndrome; diagnostic tests; sensitivity and specificity; reproducibility; epidemiological research; telephone interviews

Abstract

Background. There is need in large epidemiological studies of Restless Legs Syndrome (RLS) for an instrument that may be administered by non-clinicians to identify persons who are likely RLS cases. We evaluated the accuracy and reproducibility of the Johns Hopkins Telephone Diagnostic Interview (TDI) for that purpose.

Methods. Study members were veterans recruited at a VA outpatient clinic. They had previously been administered the TDI by a trained non-clinician (Time 1). A nurse readministered the TDI, face to face (Time 2). The gold standard diagnostic interview was conducted by a physician. We calculated the reproducibility of the TDI between two administrations, and the sensitivity and specificity relative to the gold standard.

Results. Eighty-five (39%) of eligible patients completed both TDI's and 74 (34%) completed the diagnostic interview. Reproducibility was low (kappa = 0.34, $p<.01$), but was higher for interviews repeated within one year (kappa = 0.55, $p< .01$). By gold standard, 43% were definite cases and 11% were probable cases. Including those reporting => 3 symptoms as cases, sensitivity of the TDI ranged from 63% (Time 1) to 75% (Time 2). Specificity ranged from 88% (Time 1) to 71% (Time 2).

Conclusions. The sensitivity and specificity reported here are lower than previously reported. The lower accuracy may result from differences in method of administration in epidemiological versus clinical studies. The moderately high specificity allows investigators to conclude that persons who respond positively to the TDI have a high probability of RLS.

1. Introduction.

The diagnosis of Restless Legs Syndrome (RLS) is based on the patient's symptoms and history, as RLS cannot be detected by physical examination. However, physical examination may be used to rule out conditions which may mimic the symptoms of RLS.(1) A standardized diagnostic instrument may assist in organizing the examination of the patient.

In addition to diagnostic tools, there is need for an accurate screening instrument that may be used in epidemiological studies or to prescreen patient complaints. Such a screening instrument could be used to identify persons who have a high probability of being RLS cases. The Johns Hopkins telephone diagnostic interview (TDI) for RLS is a structured diagnostic interview that was developed using criteria developed by NIH consensus conference.(2) These criteria are: 1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; 2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as sitting or lying down; 3) the urge to move or unpleasant sensations are partially or totally relieved by movement, at least as long as the activity continues; 4) the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.(3)

Hening and colleagues reported that the TDI was able to distinguish previously diagnosed RLS patients from disease free controls with sensitivity = 97% and specificity = 92%. The inter-rater reliability was high (ICC = 0.95).(2) However, an accompanying editorial noted that the external validity of those results was limited to previously diagnosed RLS patients when interviewed by

an expert diagnostician. The editorial called for additional information on reliability and external validity.(4)

In the contexts of screening or epidemiological research, trained non-physicians might administer the TDI to previously undiagnosed patients with mild to moderate symptoms. Such patients might have a variety of comorbid conditions. In this paper, we report, first, the accuracy of the TDI using expert clinical diagnosis as the gold standard and, second, the reproducibility when administered at two time points by non-physician interviewers to outpatients in a primary case setting.

2. Methods

2.1 Subjects

Study members were United States military veterans who were registered to receive primary care at the Louis B. Stokes Cleveland Veterans Affairs Medical Center (VAMC) in northeastern Ohio. All had previously participated in the Veterans' Sleep Study (VSS). The VSS investigated the prevalence and outcomes of RLS among veterans. For the VSS, 1761 veterans were recruited at the time of a primary care office visit and were interviewed by telephone within one month of recruitment by trained non clinical personnel.

2.2 Data collection

The telephone interview for the VSS included measures of insomnia and daytime sleepiness, the Johns Hopkins TDI, and measures of quality of life, mental health, and health care utilization. Study members who reported RLS symptoms were asked if they had potential causes of

secondary RLS (nerve damage in legs or feet, anemia or iron deficiency, kidney failure, or pregnancy) when they developed symptoms. VA inpatient and outpatient databases were searched for potential contributors to RLS (chronic kidney disease, renal failure, folic acid disorder, iron deficiency anemia, pernicious anemia, neuritis, neuropathy, rheumatoid arthritis, Parkinson's disease, basal ganglion disorders and SSRI use). We designated the VSS telephone interview as Time 1 interview data.

The evaluation of the TDI was limited to a subgroup of VSS participants who obtained their primary care at the Community Based Outpatient Clinic (CBOC) of the Cleveland VAMC located in Akron, Ohio. These veterans were recruited for this evaluation study when they had an office visit between August, 2004 and April, 2006. A nurse administered the TDI a second time in a face to face interview. We designated the evaluation interview as Time 2 interview data. Persons who reported RLS symptoms at Time 1 interview were over-sampled for the Time 2 interview.

2.3 Gold standard

Following the Time 2 interview, study members received a diagnostic examination with a physician expert in the diagnosis of RLS (MPP). The physician was blinded to the results of the previous interviews. Using patient history, physical examination, and review of the medical record, the following information was obtained: RLS clinical features; symptom severity; contributing medical history; behavioral risk factors; family history; and medications for RLS, insomnia, and other psychotropic medications. A determination of RLS status (definite,

probable, none); and primary or secondary etiology of RLS was made. Indeterminate diagnoses were submitted for further review by an expert clinical panel.

The research was approved by the Institutional Review Boards for the Protection of Human Subjects of the participating institutions and the funding agency. Informed consent of all study members was obtained after a full explanation of the study procedures.

2.4 Data analysis

The Time 1 and Time 2 TDI were coded using the same computerized algorithm. The TDI was scored 0 through 4 indicating the number of criterion symptoms endorsed by the study member. Persons who endorsed all 4 symptoms were judged "definite" cases and persons who endorsed 3 symptoms were judged "probable" cases by questionnaire. Persons who indicated that the feelings in their legs were always caused by cramps were judged non-cases. A measure of symptom severity was based on the number of symptomatic days per month (1 day a month; 2 to 4 days a month; 5 to 15 days a month; 16 to 25 days a month; every day).

Data were analyzed using SAS, Version 9.1.(5) We measured the reproducibility of the TDI by comparing the number of symptoms endorsed at Time 1 and Time 2 using the kappa statistic with Fleiss-Cohen weights to evaluate the data.(6)

Using the physician diagnosis as the gold standard, we calculated the sensitivity and specificity and associated 95% confidence intervals (CI) for Time 1 and Time 2 TDI. Confidence intervals were calculated using an adjusted Wald method.(7) We explored the effect of presumed primary

or secondary etiology of RLS symptoms and of the time interval between interviews using stratification.

3. Results.

Two hundred eighteen patients who had participated in the VSS and received care at the Akron CBOC were eligible for this study. Eight-five (39%) completed the face-to-face Time 2 TDI. The other 133 (61%) potential study members either died prior to contact (2), left the office without speaking to the study recruiter (40) or declined to participate (91). Seventy-four (34% of 218) completed both the Time 2 TDI and the diagnostic examination. Eleven patients did not undergo diagnostic examination for the following reasons: death (1); refused examination (5); examination was not scheduled (1); judged inappropriate for study by physician (2); failed to return for examination (2).

Table 1 shows the demographic characteristics and health status of the study participants. The small proportion of women and older average age was typical of the US veteran population at the time when the VSS was initiated. The high prevalence of co-morbid health conditions was also characteristic of patients of the VA health care system.

Table 2 shows the clinical characteristics of RLS cases at Time 1 and Time 2 TDI and by the gold standard interview. At Time 1, 42% of study members met 3 or more criteria for RLS. Forty-two percent of those who reported symptoms experienced them 5 or more days each month. At Time 2, 53% of respondents met 3 or more criteria, and 58% experienced symptoms 5 or more days each month. From medical record and interview data, 34 (40%) of study

members had one or more co-morbid conditions or medication that has been associated with RLS (potential secondary RLS). Sixteen study members (19%) had a sleep diagnosis in their medical record, including one RLS diagnosis. At diagnostic examination, 32 respondents (43%) were judged to be definite RLS and 8 respondents (11%) were judged probable RLS. The examining physician judged 20 cases to be primary RLS; 15 cases to be secondary RLS; and for 5 cases primary or secondary status could not be determined.

The mean interval between Time 1 and Time 2 interview was 13.9 months (SD = 5.8 months). Agreement on the number of reported symptoms at Time 1 and Time 2 TDI was kappa = 0.34 ($p<0.01$). Agreement among the 29 study members (34%) whose Time 2 interview occurred within one year of the Time 1 interview was higher (kappa = 0.55) than among those whose Time 2 interview was delayed (kappa = 0.23). However, the kappa statistics were not statistically different ($\chi^2 = 2.77$, $p = 0.10$). We also stratified the sample based on the presence or absence of RLS related comorbid conditions in the medical record (see Table 2). There was no difference in agreement ($\chi^2 = 0.68$, $p = 0.41$) between those with (n = 34, kappa = 0.34) or without (n = 51, kappa = 0.27) RLS related comorbidities.

The interval from Time 1 TDI to gold standard diagnostic examination averaged 15.6 months (standard deviation, 5.7 months). Twenty-three percent of diagnostic examinations were completed within one year of Time 1 TDI. Seventy-three percent of diagnostic examinations were completed within one year of the Time 2 interview (mean = 1.1 months, standard deviation = 2.1 months). Twenty-one (28%) of the diagnostic examinations were conducted on the same day as the Time 2 interview.

Table 3 shows the evaluation of the TDI using 3 different rules for the RLS case definition. We evaluated rules that required: definite cases only; definite and probable cases; or definite and probable case with symptoms at least 2 to 4 days monthly. The obtained sensitivity for the Time 1 TDI ranged from 44% to 63% with specificity ranging from 83% to 88%. Sensitivity for Time 2 TDI ranged from 56% to 75% with specificity ranging from 71% to 81%. For Time 1 TDI data, the best balance of sensitivity (63%) and specificity (88%) was obtained by including both probable and definite cases with no requirement for disease severity. Applying the same rule to Time 2 data resulted in a sensitivity = 75% with a specificity = 71%.

We also used the Time 1 data to develop the rule which best maximized both sensitivity and specificity. We then used Time 2 data to evaluate the resulting rule. This case definition was: any 3 symptoms; or the two symptoms (1) uncomfortable/unpleasant feelings in legs or an urge to move accompanied by (2) feelings relieved by walking. This rule had sensitivity = 75% with specificity = 74% using Time 1 data, and sensitivity = 75% with specificity = 71% using Time 2 data.

We hypothesized that persons with secondary RLS might, over time, have a change in their symptoms due to changes in their underlying condition. Stratification by possible primary and secondary etiology of RLS and by time from TDI to diagnostic examination did not show any differences between the subgroups on the accuracy of the questionnaire.

4. Discussion.

Hening and colleagues initially reported that the TDI had a sensitivity of 97% and specificity of 92% in a sample of previously diagnosed RLS cases and known disease free controls.(2) The same research group conducted a second evaluation of the TDI among family members of participants in a case-control study of RLS. These family members, who were not patients, were interviewed by an expert clinician using the TDI, followed by blinded clinical interviews. The interview format allowed additional clarifying questions at the discretion of the clinician interviewer. The resulting sensitivity was at least 90% and the specificity was at least 91%. (8)

In our analysis of veterans recruited at a primary care visit, we find the sensitivity and specificity to be substantially lower than reported above. While the sensitivity improved from 63% at Time1 to 75% at Time 2, the specificity decreased from 88% to 71%. There are several possible explanations for the discrepancy between our findings and previous reports. The participants in our study were primary care patients of the VA health care system who were interviewed by a trained non-clinician at Time 1 and by a nurse at Time 2. Only one study member had previously received an RLS diagnosis. It is known that, in contrast to diagnosed cases, previously undiagnosed patients will have a symptom distribution that overlaps more with the symptoms of non-cases. The increased overlap of symptom distributions results in increased numbers of false positive and false negative tests.(9)

We have assessed the characteristics of the 1761 veterans included in the Veterans Sleep Study and found that they are representative of patients who make 4 or more VA outpatient visits a year. Review of medical records found a large number of comorbid health conditions including

RLS mimics. Possible RLS mimics found were akathisia (3), cramps (1), limb pain (11), myalgia/ myositis (2), neuralgia (1), neuropathy (9), arterial insufficiency (9), B complex deficiency/ burning feet syndrome (4), and paresthesia (1). We speculate that such patients may experience and report their symptoms in a way that results in a relatively lower accuracy of the interview.

Although our interviewers had received training regarding sleep disorders with an emphasis on RLS and had been trained extensively in the use of the TDI, they did not have a clinical background in the diagnosis and treatment of RLS. The interviewers were provided with additional language to characterize the feelings of leg discomfort. Other than that, they followed the questionnaire in a standardized manner and encouraged study members to give their best response to each question. Thus, our methods differed from previous reports both in the qualifications of the interviewers (trained interviewers versus expert clinicians) and the manner of administration (structured versus semi-structured interview).

For both Time 1 and Time 2 data, requiring endorsement of all 4 symptoms or more frequent symptoms, resulted in unacceptable loss of sensitivity. In contrast, the empirical alternate rule that we developed maximized both sensitivity and specificity in this patient sample.

The data reported here indicate that the TDI can be useful in epidemiologic investigations of RLS among primary care patients and may be used to screen patient complaints. The specificity of the TDI at Time 1 interview was adequate (88%). This level of specificity allows a conclusion that positive respondents have a high probability of RLS. The relatively low sensitivity (63%)

suggests that there will be additional RLS cases which are undetected by the TDI. As there was a mean of 15.6 months from Time 1 interview to clinical diagnosis, these findings may represent a lower boundary of the accuracy of the TDI in practice.

The reproducibility of TDI, including all observations was low (kappa = 0.34), but improved (kappa = 0.55) when the analysis was restricted to interviews conducted within a year. Landis and Koch have characterized kappa statistics between 0.20 and 0.40 as fair agreement beyond chance and statistics between 0.41 and 0.60 as moderate agreement.(10) The modest agreement between the two interviews may result in part from the research design. Time 1 interviews were conducted by telephone, while Time 2 interviews were conducted face to face. Thus, in addition to the passage of time, both personnel and method varied between interviews. We speculate that the values reported here may represent a lower bound of the expected reliability of the TDI.

Our study has several limitations. The high level of co-morbidity among VA patients limits the generalizability to patients with similar characteristics. While only one patient had a diagnosis of RLS in the VA medical record, we do not know if others had complained of RLS symptoms to their physician and what discussion had ensued. VA patients also consult physicians outside of the VA and we did not have access to outside medical records. However, no study member reported a diagnosis of RLS during the interview. The Time 1 interviews occurred before FDA approval of medication for RLS and it is unlikely that study members were aware of RLS as a potential diagnosis.

The 2003 NIH consensus report suggested a uniform set of criteria to be used in epidemiological studies. The report comments on the paucity of empirical data on the sensitivity and specificity of instruments which operationalize these criteria in the context of large scale epidemiological studies.(3) Since the publication of consensus criteria, the use of these criteria for case identification in epidemiologic research has become standard. However, few authors have published the specifics of the diagnostic interviews used in their research, including data on the accuracy of the instruments. Because of the interest in quantifying the prevalence of RLS, especially in primary care and community populations, rigorous evaluation of questionnaires in a variety of settings is important.

Acknowledgements:

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Table 1. Demographic Characteristics of Study Participants.

		No.	%
Gender	Male	75	88
	Female	10	12
Race/ Ethnicity	White	76	89.4
	African American	6	7.1
	Native American	4	4.7
	Asian American	1	1.2
Co-morbid health conditions	RLS mimic condition	28	32.9
	Psychosis	17	20.0
	Depression	30	35.3
	Malignant neoplasm	11	12.9
	Thyroid disease	7	8.2
	Obesity (BMI $\geq$ 30)	27	31.8
	Diabetes	37	40.0
	Lipid disorder	61	71.8
	Hypertension	50	58.8
	Ischemic heart dis.	34	40.0
	Cerebrovascular dis.	19	22.4
	COPD	25	29.4
Age	Mean 63.1	SD, 15.1; Range 27 - 88	

Table 2. RLS Status and Related Clinical Characteristics of Study Participants.

	Time 1 Interview, n = 85		Time 2 Interview, n= 85	
	No.	%	No.	%
RLS Criteria By TDI				
4 Symptoms	28	32.9	30	35.3
3 Symptoms	8	9.4	15	17.6
0 to 2 Symptoms	49	57.6	40	47.1
Frequency RLS Symptoms / Month				
Everyday	14	16.5	24	28.2
16 to 25 days	1	1.2	11	12.9
5 to 15 days	21	24.7	14	16.5
2 to 4 days	14	16.5	20	23.5
< 2 days	35	41.2	16	18.8
RLS by Clinical Examination, n = 74				
Definite			32	43.2
Probable			8	10.8
None			34	45.9
Conditions associated with RLS [a]				
Anemia	3	3.5		

Table 2. RLS Status and Related Clinical Characteristics of Study Participants. *Continued*

	Time 1 Interview, n = 85		Time 2 Interview, n= 85	
	No.	%	No.	%
Conditions associated with RLS [a] *Continued*				
Nerve damage	11	12.9		
Parkinson's disease	0	0.0		
Kidney disease	4	4.7		
SSRI use	21	24.7		
More than one condition present	5	5.9		
Sleep diagnoses [a]				
RLS	1	1.2		
Organic insomnia	1	1.2		
Sleep disturbance, unspec.	2	2.4		
Other Insomnia	2	2.4		
Other & unspec, sleep apnea	10	11.8		
Other hypersomnia	2	2.4		
Hypersomnia with apnea	6	7.1		
Other sleep disturbance	2	2.4		
More than one sleep diagnosis	10	11.8		

[a] Data are from patient medical records and were obtained at Time 1 only.

Table 3. Accuracy of the TDI at Time 1 and Time 2 interview using clinical interview as the gold standard.

Case Criterion (TDI)	Time 1 TDI		Time 2 TDI	
	Sensitivity % (95% C.I.)	Specificity % (95% C.I.)	Sensitivity % (95% C.I.)	Specificity % (95% C.I.)
Definite Cases [a]	44 (28, 61)	83 (69, 92)	56 (39, 72)	81 (66, 90)
Definite or Probable Cases [b]	63 (47, 76)	88 (73, 96)	75 (60, 86)	71 (54, 83)
Definite or Probable Cases, $\geq$ 2-4 days each month [b]	55 (40, 69)	88 (73, 96)	73 (59, 87)	74 (57, 85)

[a]Gold standard cases are definite cases by clinical interview

[b]Gold standard cases are probable and definite cases by clinical interview.

Appendix D. Bibliography of Published Abstracts

Ober, SK, Bourguet, CC, Baughman, KR, Steiner, RP, Shapiro, HD. The Prevalence and Outcomes of Restless Legs Syndrome among Veterans. Sleep, 2004; 27: A310.

Bourguet CC, Steiner RP, Ober SK, Baughman KR, Shapiro HD. Insomnia and Daytime Sleepiness: Risk Attributable to RLS, BMI, Smoking, and Alcohol in a VA Outpatient Population. American Journal of Epidemiology, 2005; 161(S1): S90.

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Baughman KR, Bourguet CC, Ober SK, Steiner RP, Shapiro HD. Insomnia and Daytime Sleepiness: Risk Attributable to RLS, BMI, Smoking, and Alcohol in a VA Outpatient Population. Sleep, 2005; 28:A276.

Bourguet CC, Ober SK, Steiner RP, Baughman KR, Panzner MP. Accuracy and Reproducibility of the Johns Hopkins Telephone Diagnostic Instrument for Restless Legs Syndrome. Sleep, 2007; 30: A288.

Baughman KB, Bourguet CC, Ober SK, Steiner RP. The Association of Antidepressant Use with Restless Legs Syndrome in a VA Outpatient Population. Sleep, 2007; 30: A291.

Appendix E. Presentations made at NEOUCOM

Population Attributable Fractions

Lessons from the CDC's attempt to estimate mortality due to obesity

Questions to Answer

- What is a Population Attributable Fraction?
- How are they used?
- How are they misused?
- What are the implications for public health programs?

- Examples to understand the use and misuse of attributable fractions
  - Excess deaths associated with obesity
  - Restless Legs Syndrome as a risk factor for Insomnia

- Use of PAF not always clear cut
  - Mokdad, et al. (2004)
  - Estimated **365,000 deaths** due to being overweight
  - Flegal, et al. (2005)
  - Estimated only **26,000 deaths** to being overweight
  - Who should we believe?

Population Attributable Fraction

- Also referred to as the population attributable risk, population attributable risk percent, etiological fraction, and the excess fraction.
- The fraction of disease cases in a population associated with an exposure (or a group of exposures).

The Question:

- How much of the disease burden in a population could be eliminated if the effects of certain causal factors were eliminated from the population?
- What are the implications for a realistic and effective prevention strategy?

Population Attributable Fraction =

$$\frac{\text{Prob (Disease in population) - Prob (Disease in unexposed)}}{\text{Prob (Disease in population)}}$$

OR, you can use the relative risk...

$$\frac{\text{Prevalence of exposure x (Relative Risk -1)}}{\text{1+ Prevalence of exposure x (Relative Risk-1)}}$$

Levin 1953

Proportion of cases exposed to a risk factor $\left(\frac{RR-1}{RR}\right)$

Kleinbaum et al. 1982

Relative Risk

- The likelihood of developing the disease in the exposed group relative to those who are not exposed.

$$RR = \frac{\text{Probability (Disease in exposed)}}{\text{Probability (Disease in unexposed)}}$$

How are they used?

- 2004 JAMA article "Actual Causes of Death in the United States, 2000"

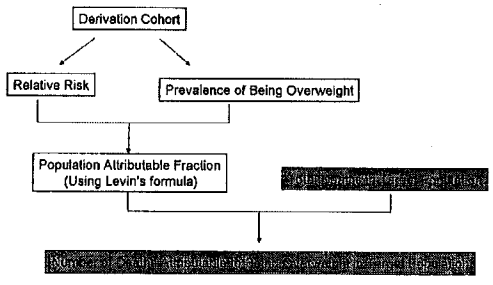
  Mokdad, Marks, Stroup, & Gerberding

  - Estimated 365,000 deaths due to being overweight (a BMI > 25)
  - Concluded that being overweight was almost as important as smoking as a mortality risk factor

Other Risk Factors

Risk Factor	Number of Deaths
Smoking	435,000
Overweight	365,000
Alcohol Consumption	85,000
Microbial agents	75,000
Toxic agents	55,000
Motor Vehicle	43,000
Firearms	29,000
Sexual Behavior	20,000
Illicit Drug Use	17,000
Total	1,159,000

How did Mokdad et al. estimate deaths?



One year later...

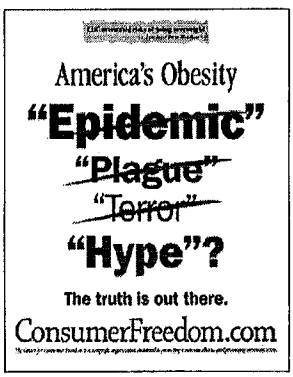
- **2005 JAMA article "Excess Deaths Associated With Underweight, Overweight, and Obesity"**
  Flegal, Graubard, Williamson, & Gail
  - Estimated that only 111,909 due to obesity (BMI>30)
  - Being overweight (BMI 25-29) is "protective", -86,094 deaths
  - 25,815 deaths due to being overweight or obese

Estimates with Confidence Intervals

Mokdad et al.
Reference Group 23-25
Overweight/Obese BMI > 25 **365,000 excess deaths**

Flegal et al.

Underweight BMI < 18.5	33,746 deaths (CI: 15,726 to 51,766)
Reference Group 18.5-25	
Overweight BMI 25-30	-86,094 deaths (CI: -161,223 to -10,966)
Obese BMI > 30	**111,909 deaths (CI: 53,754 to 170,064)**



Institute of Medicine Workshop: Estimating the Contributions of Lifestyle-Related Factors to Preventable Death

- Main objective: improve the methodology used to quantify and interpret lifestyle contributions to preventable death.

http://www.nap.edu/catalog/11323.html

Differences in studies

Mokdad et al.	Flegal et al.
➢"Partially adjusted" for age	➢Stratified by age

Weighted sum method

Group	N	P(E)	RR	No. of deaths	PAF	Excess deaths
A	1000	.5	2	150	.333	50
B	500	.1	2	165	.091	15
Sum						65

http://www.cdc.gov/nchs/ppt/bsc/flegal.ppt

Weighted sum method

Group	N	P(E)	RR	No. of deaths	PAF	Excess deaths
A	1000	.5	2	150	.333	50
B	500	.1	2	165	.0909	15
Sum						65
Total	1500	.37	2	315	.2683	84.5

"Partially adjusted" method

Differences in studies

Mokdad et al.	Flegal et al.
➢"Partially adjusted" for age	➢Stratified by age
➢RR based on 6 population studies	➢RR based only on NHANES data

Derivation Cohorts

- Alameda County Health Study
- Framingham Heart Study
- Tecumseh Community Health Study
- American Cancer Society Cancer Prevention Study I
- Nurses Health Study
- National Health and Nutrition Examination Survey I: Epidemiological Follow-up Study

Differences in studies

Mokdad et al.	Flegal et al.
➢"Partially adjusted" for age	➢Stratified by age
➢RR based on 6 population studies	➢RR based only on NHANES data
➢Used only NHANES I mortality data	➢Used mortality data from NHANES II and NHANES III

Differences in studies

Mokdad et al.	Flegal et al.
➢"Partially adjusted" for age	➢Stratified by age
➢RR based on 6 population studies	➢RR based only on NHANES data
➢Used only NHANES I mortality data	➢Used mortality data from NHANES II and NHANES III
➢Used a PAF formula not appropriate for adjusted rates.	➢Used a PAF formula appropriate for adjusted rates.

PAF Formulas

$$\frac{\text{Prevalence of exposure (Relative Risk -1)}}{\text{1+ Prevalence of exposure (Relative Risk-1)}}$$

Levin 1953

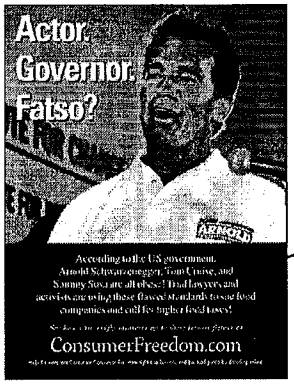
Proportion of cases exposed to a risk factor $\left(\frac{RR-1}{RR}\right)$

Kleinbaum et al. 1982

Assumptions of both studies

- Relative risks from past cohorts apply to today's population
- There are no other confounding variables
- BMI is an adequate indicator of obesity and the cut points of 18.5, 25, & 30 are most appropriate
- Association of BMI and mortality is causal.

--from Flegal et al.



"According to the U.S. government, Arnold Schwarzenegger, Tom Cruise, and Sammy Sosa are all obese!"

- To further understand these differences in the use of attributable fractions:

Illustration from the Veteran's Sleep Study

Supported by DAMD17-03-1-0082 from the US Army Medical Research and Materiel Command and an unrestricted grant from Pfizer Pharmaceutical Corporation.

Study Design

- Cross-sectional telephone survey
- 1761 veterans from Cleveland VA Medical Center
- 12 VA primary care outpatient clinics
- 80% were male, 86% Caucasian, 46% had at least some college

Goal of VA Sleep Study

- Estimate the prevalence of Restless Legs Syndrome and its effect on insomnia, mental health, and health care utilization.
  - Estimate the effect of potential risk factors (RLS, in particular) for insomnia.

Insomnia

- Difficulty initiating sleep,
- Repeated or lengthy awakenings,
- Early awakening, unable to return to sleep.

- 20% to 30% of the general population will report symptoms of insomnia at any given time.
- Primary care patients – 10% to 20% report severe insomnia.

Restless Legs Syndrome

- A need or urge to move the legs, often accompanied by unpleasant sensations;
- Sensations begin or worsen during periods of rest or inactivity;
- Totally or partially relieved with movement;
- Worse in the evening or at night.

- General population
  - 7% - any frequency of symptoms
  - 3% - moderately or severely distressing symptoms

Relative Risk

$$RR = \frac{\text{Probability (Disease in exposed)}}{\text{Probability (Disease in unexposed)}}$$

Exposure: RLS	Disease: Insomnia Yes	Disease: Insomnia No	
Yes	90 36.59%	156 63.41%	246
No	195 13.49%	1250 86.51%	1445
	285	1406	1691

$$RR = \frac{36.59}{13.49} = 2.71$$

Relative Risk

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	285	1406	1691

$$RR = \frac{36.59}{13.49} = 2.71$$

Population Attributable Fraction

- RR = 2.71
- Prevalence of RLS = 246 / 1691 = .145
- Proportion of insomnia cases with RLS = 90 / 285 = .316

$$\frac{\text{Prevalence of exposure (Relative Risk -1)}}{\text{1+ Prevalence of exposure (Relative Risk-1)}} = .20$$

Levin 1953

$$\text{Proportion of cases exposed to a risk factor} \left(\frac{RR-1}{RR}\right) = .20$$

Kleinbaum et al. 1982

Using Logistic Regression to estimate Relative Risks

$$\ln(y) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_k x_k + \varepsilon$$

$$P(\text{Insomnia}) = \frac{\exp(\alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_k x_k)}{1 + \exp(\alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_k x_k)}$$

An Example Using 1 Predictor

$$\ln(\text{Insomnia}) = -1.86 + 1.31\ \text{RLS}$$

RLS=1 $$P_1 = \frac{\exp(\alpha+\beta)}{1+\exp(\alpha+\beta)} = \frac{\exp(-1.86+1.31)}{1+\exp(-1.86+1.31)} = 0.37$$

RLS=0 $$P_0 = \frac{\exp(\alpha)}{1+\exp(\alpha)} = \frac{\exp(-1.86)}{1+\exp(-1.86)} = 0.13$$

$$RR = \frac{P_1}{P_0} = \frac{0.37}{0.13} = 2.71$$

Using Multiple Variables to estimate RR

$$\text{Log (Insomnia)} = \alpha + \beta_1 \text{RLS} + \beta_2 \text{Obesity} + \beta_3 \text{Health} + \beta_4 \text{Smoking} + \beta_5 \text{Alcohol} + \beta_6 \text{Age} + \beta_7 \text{Gender}$$

$$P_1 = \frac{\exp(\alpha + \beta_1 \text{RLS} + \beta_2 \text{Obesity} + \beta_3 \text{Health} + \ldots)}{1 + \exp(\alpha + \beta_1 \text{RLS} + \beta_2 \text{Obesity} + \beta_3 \text{Health} + \ldots)} = .22$$

$$P_0 = \frac{\exp(\alpha + \beta_1 \text{RLS} + \beta_2 \text{Obesity} + \beta_3 \text{Health} + \ldots)}{1 + \exp(\alpha + \beta_1 \text{RLS} + \beta_2 \text{Obesity} + \beta_3 \text{Health} + \ldots)} = .10$$

For the RR of RLS, you set the RLS variable to 1 for P_1 and to 0 for P_0. The other variables are all set to their mean.

$$RR_{RLS} = P_1 / P_0 = 0.22 / 0.10 = 2.12$$

Crude Relative Risk vs. Adjusted Relative Risk

- Single independent variable RR=2.71
- Multiple independent variables RR=2.12

PAF based on multivariate analysis

- RR = 2.12
- Prevalence of RLS = 246 / 1691 = .145
- Proportion of insomnia cases with RLS = 90 / 285 = .316

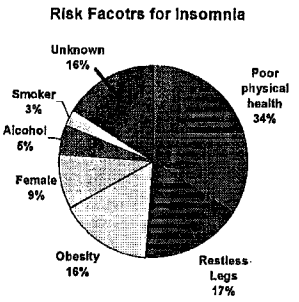
$$\frac{\text{Prevalence of exposure (Relative Risk -1)}}{\text{1+ Prevalence of exposure (Relative Risk-1)}} = .14$$

Levin 1953

$$\text{Proportion of cases exposed to a risk factor } \left(\frac{RR-1}{RR}\right) = .17$$

Kleinbaum et al. 1982

Predictor Variables	PAF
Poor Physical health	34%
Restless Legs Syndrome	17%
Obesity (BMI of 30+)	16%
Female	9%
Alcohol Dependence	5%
Currently smokes	3%
TOTAL*	84%



* Age is left out of these totals. The PAF for age was 25%.

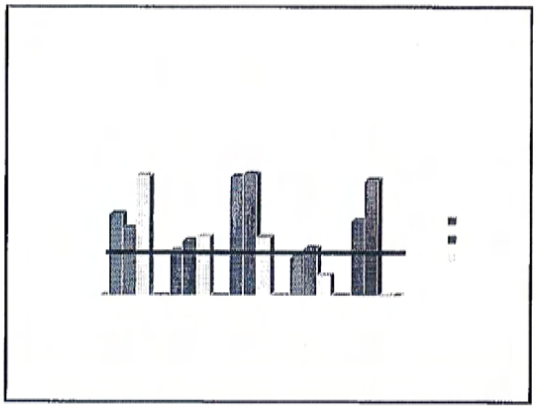
Summary Population Attributable Fraction

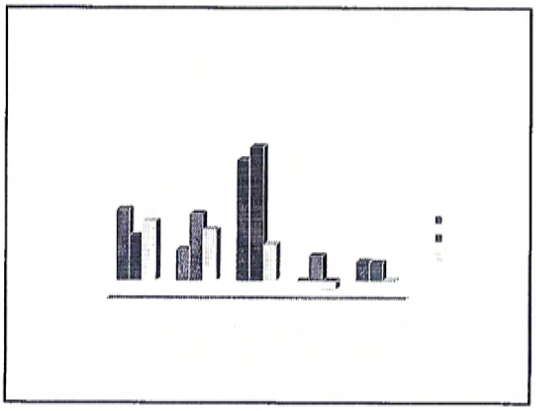
- The PAF for the combination of obesity, smoking, alcohol dependence and RLS is 42%.
- Controlled for age, gender, and health status.

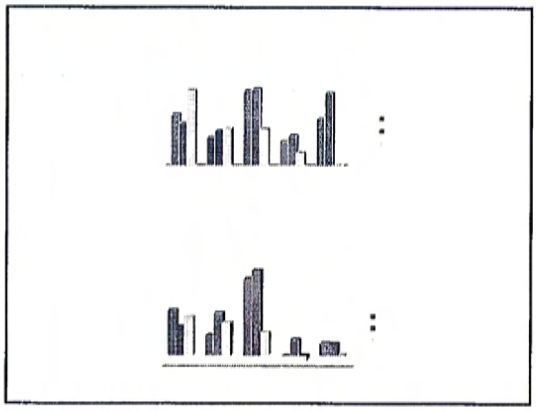
New variable: RISK
If the patient has RLS, is obese, currently smokes, OR is alcohol dependent then RISK=1.
All others coded as 0.

The Next Step

- We've calculated an adjusted PAF
  - 17% of Insomnia cases are associated with RLS
- But we haven't stratified by age, yet
- Is it necessary?
  - Does age interact with RLS?
  - Is our sample distribution similar to the population we're interested in?







Number of Insomnia cases in Cleveland VA Population Associated with RLS

Weighted Sum Method

Age Group	N	P(RLS)	RR	No. of Insomnia cases	PAF	Excess Insomnia cases
< 50	7549	.20	2.12	2040	.20	403
50-69	26,468	.18	1.75	5638	.12	701
70 +	32,351	.09	3.11	1899	.17	314
Total						1418
Total	66,368	.15	2.12	9577	.17	1598

Partially Adjusted Method

Summary of RR and PAF Calculations

	RR	PAF
Crude	2.71	.20
Partially Adjusted	2.12	.17
Weighted Sum < 50	2.12	.20
50-69	1.75	.12
> 70	3.11	.17

Lessons for Epidemiologists

- Keep up to date with changes in biostatistics
- Always look for possible interactions
- Educate the public (and the media) on the scientific "process"
- We can't wait for scientific certainty before acting.

Use of Antidepressant Medications as a Risk Factor for Restless Legs Syndrome among VA Primary Care Patients

Kristin Baughman, PhD

Grant Support: DAMD17-03-1-0082 from the US Army Medical Research and Materiel Command and an unrestricted grant from Pfizer Pharmaceutical Corporation

Diagnostic Criteria for Restless Legs Syndrome (RLS)?

- Urge to move limbs, usually accompanied or caused by uncomfortable and unpleasant feelings in the limbs
- Rest or inactivity precipitates or exacerbates symptoms
- Getting up or moving improves the sensations
- Evening or nighttime appearance or worsening of symptoms

Causality Problem

RLS → Insomnia → Depression → Antidepressant use

Depression → Antidepressant use → RLS

Criteria for Major Depression: Depressed mood, diminished interests, feelings of worthlessness, thoughts of death, weight gain or loss, *insomnia, fatigue or loss of energy, diminished concentration, mental/physical sluggishness or agitation.*

Need 5 symptoms for Major Depression

Pharmacological Treatment of RLS

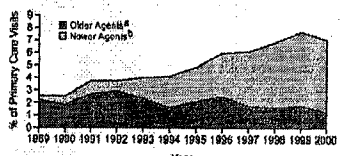
- Dopaminergic agents
- Opioids
- Benzodiazepines
- Anticonvulsants

Significance of the Problem

- RLS prevalence rates of 5% to 15% in general population
- 23% of primary care patients have a depressive disorder
- Rates of depression are higher for those with RLS
- Prevalence of antidepressant use in US primary care population is 7% (2000)

Trends in Prescribing

Figure 1. Use of Older and Newer Antidepressants in Adult Primary Care Visits



[a]Older agents include tricyclic and tetracyclic antidepressants, tricyclic and tetracyclic antidepressant combination products, monoamine oxidase inhibitors, and trazodone.
[b]Newer agents include selective serotonin reuptake inhibitors, bupropion, mirtazapine, nefazodone, and venlafaxine.

Question:

Do antidepressant medications exacerbate Restless Legs Syndrome (RLS)?

In particular, do Selective Serotonin Reuptake Inhibitors (SSRIs) exacerbate RLS symptoms?

Evidence for relationship

- Case Studies & Case Series Reports
- Cross-Sectional Population study, N=18,980 (Ohayon & Roth, 2002)

Evidence against relationship

- Retrospective Chart Review of Sleep Center patients, N= 200 (Brown et al., 2005)
- Retrospective self-reported questionnaires from patients prescribed SSRIs (Dimmitt & Riley, 2000)
- Naturalistic, prospective study of patients prescribed antidepressants, N=243 (Leutgeb & Martus, 2002)

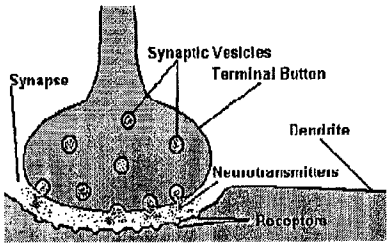
What causes RLS?

- Dopamine deficiency

What causes depression?

- Serotonin deficiency
- Norepinephrine deficiency
- Possibly a dopamine deficiency

Illustration of Neurotransmitters



http://www.pbs.org/wnet/closetohome/animation/coca-anim-main.html

From PBS website: Bill Moyers on Addiction: Close To Home

Treatment of Depression

- **SSRI:** Selective serotonin reuptake inhibitors
- **SNRI:** Serotonin and norepinephrine reuptake inhibitors
- **NDRI:** Norepinephrine and dopamine reuptake inhibitors
- **Tricyclics:** Inhibit reuptake of serotonin and norepinephrine
- **Tetracyclics:** Combined reuptake inhibitors and receptor blockers
- **MAOI:** Monoamine oxidase inhibitors

Biological Evidence for Antidepressants Reducing Dopamine Levels

- Animal studies
  - Close proximity of dopamine & serotonin neurons in striatum
  - Uptake of serotonin into dopamine neurons when SSRIs are used
  - Less dopamine available
- Human studies
  - SSRIs affect vigilance due to disruption of dopamine neurotransmission

Biological Evidence for SSRIs Increasing Dopamine Levels

- **Human Studies**
  - Positron emission tomography (PET) study, Use of SSRI increased the release of dopamine in the brain, N=8 (Tiihonen et al., 1996)

Cleveland VA Sample

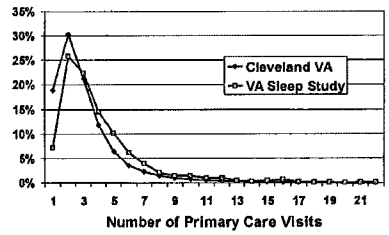
- Cross-sectional telephone survey
- 1761 veterans from Cleveland VA Medical Center
- Recruitment at 12 VA primary care outpatient clinics
- 80% were male, 91% Caucasian, 46% had at least some college

Age and Gender Distribution

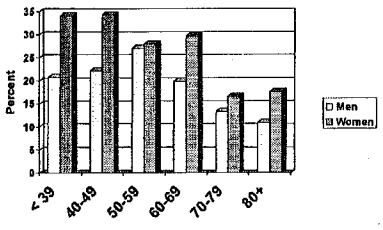
	Women	Men	All
Age 20-29	7.7% (27)	1.4% (20)	2.7% (47)
Age 30-39	12.9% (45)	3.8% (53)	5.6% (98)
Age 40-49	30.1% (105)	11.8% (167)	15.5% (272)
Age 50-59	22.4% (78)	20.3% (287)*	20.7% (365)
Age 60-69	11.2% (39)	17.9% (252)*	16.5% (291)
Age 70-79	5.4% (19)	20.0% (283)*	17.2% (302)
Age 80+	10.3% (36)	24.8% (350)*	21.9% (386)
Total	100% (349)	100% (1412)	100% (1761)

* We met our recruitment goal for these groups

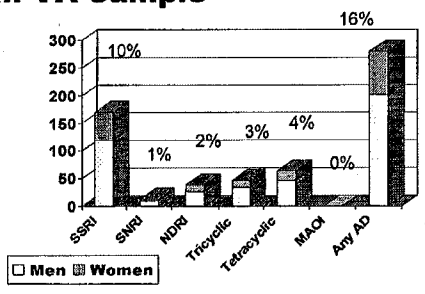
Primary Care Visits, 2004



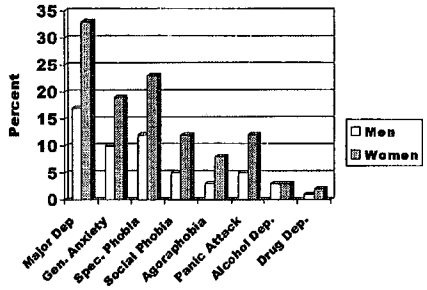
RLS Rates by Age & Gender



Current Antidepressant Use in VA Sample



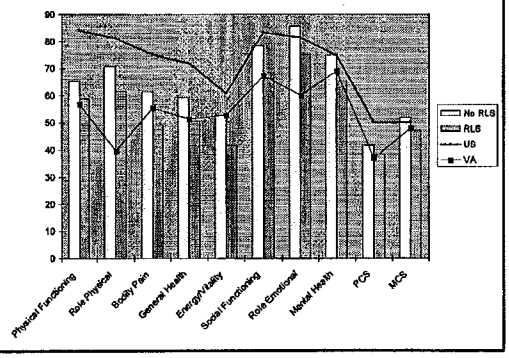
WHO Composite International Diagnostic Index (CIDI)



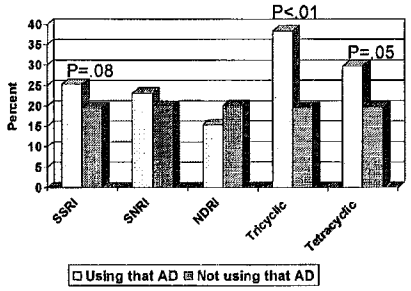
Major Depression by Antidepressant Use

	Depressed	Not Depressed
Using Antidepressants	126 36%	157 11%
Not Using Antidepressants	226 64%	1240 89%
	352	1397

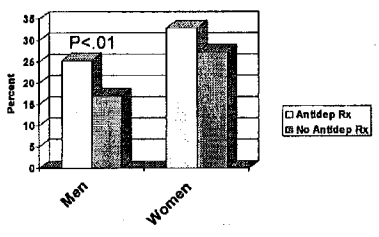
SF36 Scores



RLS Rates by Use of Antidepressants



RLS Rates by Use of a Serotonergic Antidepressant



Comparison of RLS Rates

No depression and not using antidepressants	17%
Depressed but not using antidepressants	28%
No depression but using **serotonergic antidepressants**	22%
Depressed and using **serotonergic antidepressants**	34%
No depression but using **tricyclics**	17%
Depressed and using **tricyclics**	61%
No depression but using **tetracyclics**	24%
Depressed and using **tetracyclics**	34%

Logistic Regression Predicting RLS

Variable	estimate	p	OR (95% CI)
SSRI	.11	.58	1.12 (0.76-1.65)
NDRI	-.67	.14	0.51 (0.21-1.25)
SNRI	-.19	.79	0.83 (0.21-3.22)
Tricyclic	.68	.04	1.97 (1.05-3.69)
Tetracyclic	.19	.54	1.20 (0.67-2.18)
Serotonergic Antidepressant	.24	.14	1.28 (0.93-1.76)

Controlled for race, age, gender, BMI, and smoker.

Combinations of Antidepressants

- NDRI and Tetracyclic N=9
- SSRI and Tetracyclic N=20
- SSRI and Tricyclic N=8
- SSRI and NDRI N=8

Controlling for Mental Health

Variable	B estimate	p	Odds Ratio (95% CI)
Original model			
NDRI	-.67	.14	0.51 (0.21 - 1.25)
Tricyclic	.68	.04	1.97 (1.05 - 3.69)
Controlled for CIDI Major Depression			
NDRI	-.77	.10	0.47 (0.19 - 1.14)
Tricyclic	.60	.07	1.82 (0.96 - 3.44)
Controlled for SF36 MH subscale			
NDRI	-.91	.05	0.40 (0.16 - 1.00)
Tricyclic	.56	.09	1.76 (0.92 - 3.34)
Controlled for SF36 MCS composite score			
NDRI	-.96	.04	0.38 (0.15 - 0.96)
Tricyclic	.63	.06	1.88 (0.98 - 3.62)

Conclusion

- Certain antidepressants have a negative impact on RLS symptoms.
  - Biological explanations for relationship
  - Specific antidepressants (tricyclics)
  - Relationship remains when controlling for levels of depression or mental health

Limitations

- Retrospective
- High number of comorbidities in VA data
- Need to control for dosage of antidepressants

Strengths

- Large data set (n=1761)
- Primary Care sample
- Prescription data complete
  - VA has an affordable program so veterans tend to fill all their prescriptions at the VA
  - Computerized medical records
- VA sample has higher rates of depression and RLS than general population

Appendix F. Personnel receiving salary support.

Principal Investigator – Claire C. Bourguet, Ph.D. Northeastern Ohio Universities College of Medicine

Co-Investigator – Richard P. Steiner, Ph.D. The University of Akron.

Study Coordinator – Kristin R. Baughman, Ph.D. Louis B. Stokes Cleveland VA Medical Center and the Northeastern Ohio Universities College of Medicine

Consultant – Howard Shapiro, M.D. Akron General Medical Center

Consultant – Frank Bosso, Ph.D. The Youngstown State University

Secretarial Support – Kali Williams; Diane Kehner, Northeastern Ohio Universities College of Medicine.

Patient recruiter / Interviewer – Joanna Benson; Rebecca Chase; Ruth Einsporn; Jantene Johnson; Tanya Tomblin; Courtney Vierstra, Louis B. Stokes Cleveland VA Medical Center.